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(54) Thiazolidinone derivatives as hypoglycemic agents and for treating Alzheimer's disease.

(57) Provided are methods for treating hyperglycemia and Alzheimer's disease utilizing certain rhodanine derivatives. Certain of the rhodanine derivatives utilized in the instant methods are novel and, accordingly, such compounds, process for preparing same and pharmaceutical formulations thereof, are also provided.

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The present invention relates to certain rhodanine derivatives, pharmaceutical formulations thereof, processes for preparing same, as well as methods of using such compounds to treat Alzheimer's disease and hyperglycemia.

Diabetes mellitus is a systemic disease characterized by disorders in the metabolism of insulin, carbohydrates, fats and proteins, and in the structure and function of blood vessels. The primary symptom of acute diabetes is hyperglycemia, often accompanied by glucosuria, the presence in urine of large amounts of glucose, and polyuria, the excretion of large volumes of urine. Additional symptoms arise in chronic or long standing diabetes. These symptoms include degeneration of the walls of blood vessels. Although many different organs are affected by these vascular changes, the eyes and kidneys appear to be the most susceptible. As such, long-standing diabetes mellitus, even when treated with insulin, is a leading cause of blindness.

There are two recognized types of diabetes. Type I diabetes is of juvenile onset, ketosis-prone, develops early in life with much more severe symptoms and has a near-certain prospect of later vascular involvement. Control of this type of diabetes is difficult and requires exogenous insulin administration. Type II diabetes mellitus is of adult onset, ketosis-resistant, develops later in life, is milder and has a more gradual onset.

One of the most significant advancements in the history of medical science came in 1922 when Banting and Best demonstrated the therapeutic effects of insulin in diabetic humans. However, even today, a clear picture of the basic biochemical defects of the disease is not known, and diabetes is still a serious health problem. It is believed that two percent of the United States' population is afflicted with some form of diabetes.

The introduction of orally effective hypoglycemic agents was an important development in the treatment of hyperglycemia by lowering blood glucose levels. Oral hypoglycemic agents are normally used in the treatment of adult onset diabetes.

A variety of biguanide and sulfonylurea derivatives have been used clinically as hypoglycemic agents. However, the biguanides tend to cause lactic acidosis and the sulfonylureas, though having good hypoglycemic activity, require great care during use because they frequently cause serious hypoglycemia and are most effective over a period of ten years.

In Chemical & Pharmaceutical Bulletin, 30, 3563 (1982), Chemical & Pharmaceutical Bulletin, 30, 3580 (1982) and Chemical & Pharmaceutical Bulletin, 32, 2267 (1984), reference is made to a variety of thiazolidinediones which have blood glucose and lipid lowering activities. Antidiabetic activity of ciglitazone was also reported in Diabetes, 32, 804 (1983). However, these compounds have proven difficult to use because of insufficient activities and/or serious toxicity problems.

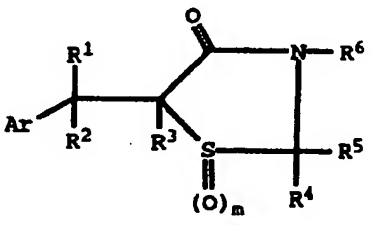
Furthermore, Alzheimer's disease, a degenerative disorder of the human brain, continues to afflict more and more persons throughout the world. Such disease results in progressive mental deterioration manifested by memory loss, confusion, disorientation and the concomitant loss of enjoyment of life associated therewith. At the present time there is no scientifically recognized treatment for Alzheimer's disease. Because of this, and because of the debilitating effects of the disease, there continues to exist an urgent need for effective treatments.

The present invention relates to a series of hypoglycemic agents which are capable of lowering blood glucose levels in mammals. Accordingly, one object of the present invention is to provide compounds having excellent hypoglycemic activity. The hypoglycemic agents of the present invention are believed to have minimal toxicological effects. It is, therefore, believed that the compounds of the present invention may be very useful for treating diabetes.

The present invention also relates to a series of compounds having cathepsin inhibitory activity. As will be discussed more fully below, compounds capable of inhibiting cathepsin (and, in particular, cathepsin D) may be useful for treating Alzheimer's disease. Accordingly, a further object of the present invention is to provide compounds which can be used to treat Alzheimer's disease.

Other objects, features and advantages of the present invention will become apparent from the subsequent description and the appended claims.

The present invention provides a method of reducing blood glucose concentrations in mammals comprising administering a therapeutically effective amount of a compound of formula (I)



(I)

wherein:

Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, trifluoromethyl, C_1-C_4 alkylphenyl, phenyl, NO_2, F, Cl, hydroxy, phenoxy, C_1-C_4 alkyloxyphenyl, thiophenyl, C_1-C_4 alkylthiophenyl, -$COOR^7$, -$N(R^7)SO_2R^7$ or -$N(R^7)_2$, where each R^7 is independently hydrogen or C_1-C_6 alkyl, (iii) 1- or 2-naphthyl, (iv) 2- or 3-benzofuranyl, (v) 2- or 3-benzothiophenyl, (vi) 2-, or 3-thienyl, (vii) 2-, 3- or 4-pyridyl, (viii) 2- or 3- furanyl, (ix) 1,3-benzodioxanyl, (x) substituted 1,3-benzodioxanyl, (xi) quinolinyl, (xii) 2- or 3-indolyl or (xiii) N-substituted 2- or 3- indolyl;

R^1 is C_1-C_6 alkyl, C_1-C_4 alkylphenyl, hydrogen, phenyl or phenyl substituted with one or two substituents independently selected from Cl, Br, F, I, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, trifluoromethyl, -NH_2, -$NH(C_1$-C_4 alkyl), -$N(C_1$-C_4 alkyl)$_2$ or C_1-C_4 alkylthio;

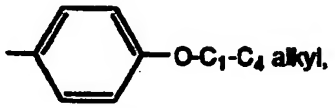
R^2 and R^3 are each hydrogen or when taken together form a bond;

R^4 and R^5 are each hydrogen or when taken together are =S, or when one of R^4 and R^5 is hydrogen, the other is -SCH_3;

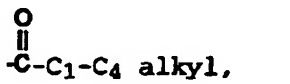
R^6 is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, -SO_2CH_3, or -$(CH_2)_p$-Y where p is 0, 1, 2, or 3 and Y is

cyano, -OR^6,

tetrazolyl, -$NR^{10}R^{11}$, -SH, C_1-C_4 alkylthio, or



where R^8 is hydrogen, C_1-C_4 alkyl or



R^9 is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy or NH_2, and R^{10} and R^{11} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, C_1-C_4 alkylphenyl, -$(CH_2)_q$OH, -$(CH_2)_q N(C_1$-C_4 alkyl)$_2$, or -$(CH_2)_q S(C_1$-C_4 alkyl), where q is an integer from 1 to 6, both inclusive, or R^{10} and R^{11}, taken together with the nitrogen atom to which they are attached, form a morpholinyl, piperidinyl, piperizinyl, or N-methylpiperazinyl ring; and

m is 0, 1, or 2;

with the provisos that

Ar cannot be phenyl substituted solely with one chloro substituent at the 4-position of the phenyl ring;

Ar cannot be phenyl substituted with a COOH moiety at the 2-position of the phenyl ring;

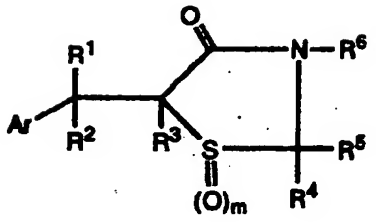
when Ar is phenyl substituted with two ethoxy moieties at the 3- and 4-positions of the phenyl ring, R^1 must be hydrogen;

Ar cannot be phenyl substituted solely with two hydroxy substituents; and

when R^4 and R^5 are each hydrogen, R^6 cannot be C_1-C_6 alkyl,

or a pharmaceutically acceptable salt thereof, to a mammal in need of having its blood glucose concentration reduced.

The present invention also provides a method of treating Alzheimer's disease in a mammal suffering from or susceptible to such disease comprising administering a therapeutically effective amount of a compound of formula (Ia)



(Ia)

wherein:

Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, trifluoromethyl, C_1-C_4 alkylphenyl, phenyl, NO_2, F, Cl, hydroxy, phenoxy, C_1-C_4 alkyloxyphenyl, thiophenyl, C_1-C_4 alkylthiophenyl, $-COOR^7$, $-N(R^7)SO_2R^7$ or $-N(R^7)_2$, where each R^7 is independently hydrogen or C_1-C_8 alkyl or (iii) 1- or 2-naphthyl;

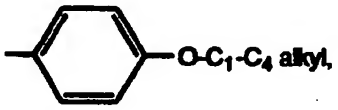
R^1 is C_1-C_8 alkyl, C_1-C_4 alkylphenyl, hydrogen, phenyl or phenyl substituted with one or two substituents independently selected from Cl, Br, F, I, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, trifluoromethyl, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$ or C_1-C_4 alkylthio;

R^2 and R^3 are each hydrogen or when taken together form a bond;

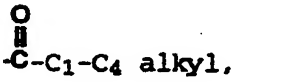
R^4 and R^5 are each hydrogen or when taken together are =S, or when one of R^4 and R^5 is hydrogen, the other is $-SCH_3$;

R^6 is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, $-SO_2CH_3$, or $-(CH_2)_p$-Y where p is 0, 1, 2, or 3 and Y is
cyano, $-OR^8$,

tetrazolyl, $-NR^{10}R^{11}$, -SH, C_1-C_4 alkylthio, or



where R^8 is hydrogen, C_1-C_4 alkyl or

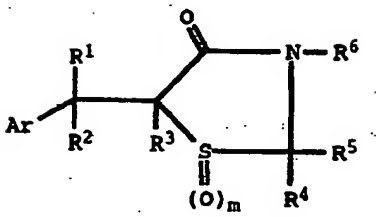


R^9 is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy or NH_2, and R^{10} and R^{11} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, C_1-C_4 alkylphenyl, $-(CH_2)_qOH$, $-(CH_2)_qN(C_1$-C_4 alkyl)$_2$, or $-(CH_2)_qS(C_1$-C_4 alkyl), where q is an integer from 1 to 6, both inclusive, or R^{10} and R^{11}, taken together with the nitrogen atom to which they are attached, form a morpholinyl, piperidinyl, piperizinyl, or N-methylpiperazinyl ring; and

m is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof, to a mammal in need of such treatment.

Certain of the compounds which can be employed in the methods of the present invention are novel. As such, the present invention also provides novel compounds of the formula (II)



(II)

wherein:

Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, trifluoromethyl, C_2-C_4 alkylphenyl, NO_2, F; Cl, phenoxy, C_1-C_4 alkyloxyphenyl, thiophenyl, C_1-C_4 alkylthiophenyl, -$COOR^7$, -$N(R^7)SO_2R^7$ or -$N(R^7)_2$, where each R^7 is independently hydrogen or C_1-C_8 alkyl, (iii) 1- or 2-naphthyl, (iv) 2- or 3-benzofuranyl, (v) 2- or 3-benzothiophenyl, (vi) 2- or 3-thienyl, (vii) 2-, 3- or 4-pyridyl, (viii) 2- or 3-furanyl, (ix) 1,3-benzodioxanyl, (x) substituted 1,3-benzodioxanyl, (xi) quinolinyl, (xii) 2- or 3-indolyl or (xiii) N-substituted 2- or 3-indolyl;

R^1 is C_1-C_8 alkyl, C_1-C_4 alkylphenyl, hydrogen, phenyl or phenyl substituted with one or two substituents independently selected from Cl, Br, F, I, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, trifluoromethyl, -NH_2, -$NH(C_1$-C_4 alkyl), -$N(C_1$-C_4 alkyl)$_2$ or C_1-C_4 alkylthio;

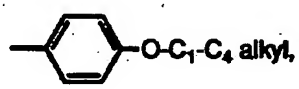
R^2 and R^3 are each hydrogen or when taken together form a bond;

R^4 and R^5 are each hydrogen or when taken together are =S, or when one of R^4 and R^5 is hydrogen, the other is -SCH_3;

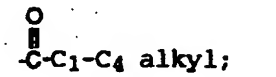
R^6 is hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_2-C_8 alkenyl, -SO_2CH_3 or -$(CH2)_p$-Y where p is 0, 1, 2, or 3 and Y is

cyano, OR^8,

tetrazolyl, -$NR^{10}R^{11}$, -SH, C_1-C_4 alkylthio or



where R^8 is hydrogen, C_1-C_4 alkyl, or



R^9 is hydrogen, C_1-C_4 alkyl or NH_2; and R^{10} and R^{11} are each independently hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, -$(CH_2)_qOH$, -$(CH_2)_qN(C_1$-C_4 alkyl)$_2$, -$(CH_2)_qS(C_1$-C_4 alkyl), C_2-C_6 alkynyl, phenyl, or C_1-C_4 alkylphenyl, where q is 1 to 6, both inclusive, or R^{10} and R^{11}, taken together with the nitrogen atom to which they are attached, form a morpholinyl, piperidinyl, piperazinyl or N-methylpiperazinyl ring; and

m is 0, 1, or 2;

with the provisos that

when Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, F, Cl, trifluoromethyl, phenoxy, C_1-C_4 alkyloxyphenyl, C_1-C_8 alkylthio, NO_2, -$N(R^7)_2$ or -$COOR^7$, where each R^7 is independently hydrogen or C_1-C_6 alkyl, (iii) 1- or 2-naphthyl, (iv) 2- or 3-benzofuranyl, (v) 2- or 3-benzothiophenyl, (vi) 2- or 3-thienyl, (vii) 2- or 3-indolyl, (viii) 2- or 3- furanyl, (ix) quinolinyl or (x) 2-, 3- or 4-pyridyl; R^1 is hydrogen or C_1-C_6 alkyl; R^2 and R^3 taken together form a bond; m is 0; and R^4 and R^5 taken together are =S, R^6 must be other than hydrogen or C_1-C_6 alkyl;

when Ar is phenyl; R^1 is hydrogen, methyl or ethyl; R^2 and R^3 taken together form a bond; m is 0; R^4 and R^5 taken together are =S; R^6 must be other than phenyl or C_1-C_4 alkylphenyl;

Ar cannot be phenyl substituted solely with one chloro substituent at the 4-position of the phenyl ring;

when Ar is phenyl substituted with two ethoxy moieties at the 3- and 4-positions of the phenyl ring, R^1 must be hydrogen;

Ar cannot be phenyl substituted with a COOH moiety at the 2-position of the phenyl ring; and

when R^4 and R^5 are each hydrogen R^6 cannot be C_1-C_8 alkyl,

and the pharmaceutically acceptable salts thereof.

In addition to the genus of novel compounds described by formula II, above, certain other of the compounds which can be employed in the methods of the present invention also appear to be novel. These compounds, while structurally similar to compounds specifically known in the art (see, for example, European Patent Application Nos. 343643, 391644 and 39817 as well as U.S. Patent No.. 4,552,891), are not actually described in any of those patents or applications. As such, the present invention also encompasses the following novel compounds and their pharmaceutically acceptable salts:

5-[(2-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(4-fluorophenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(2-thienyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(2-furanyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(3,4,5-trimethoxyphenyl)methylmethylene]-2-thioxo-4-thiazolidinone;
4-[(2-thioxo-4-thiazolidinone)methylene]benzoic acid;
5-[(3-hydroxy-4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(3-hydroxyphenyl)methylmethylene]-2-thioxo-4-thiazolidinone;
5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(3-hydroxy-4-ethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(3-ethoxy-4-propoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(3-propoxy-4-ethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(3,4-dipropoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[[3-(methyloxyphenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone;
5-[(3,5-bis(1,1-dimethylethyl)-4-hydroxy-phenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid;
5-[(3,5-dichloro-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(3-ethoxy-4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(3-ethoxy-4-methoxyphenyl)methylene)-2-thioxo-4-thiazolidinone;
5-[[3,5-bis(1-methylpropyl)-4-hydroxyphenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid;
5-[(4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-3-methyl-4-thiazolidinone;
5-[(3-methoxy-4-octoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[(3,5-dimethoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone;
5-[[3-(1,1-dimethylethyl)-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone;
5-[[3-ethoxy-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone;
5-[[3-ethoxy-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-3-methyl-4-thiazolidinone;
5-[[3-ethoxy-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid.

Certain of the above compounds and, in particular, 5-[(4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-propoxy-4-ethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-ethoxy-4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-pentoxyphenyl)methylene] -2-thioxo-4-thiazolidinone; 5-[(3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid; and 5-[[3,5-bis(1-methylpropyl)-4-hydroxyphenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid (especially the latter three compounds), appear to possess a surprising ability to lower blood glucose levels in mammals compared to structurally similar compounds known in the art. Because of such surprising activity, these compounds are particularly preferred compounds of the present invention.

In addition, 5-[[3-(1,1-dimethylethyl)-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone appears to possess a surprising ability to inhibit cathepsin D levels compared to structurally similar compounds known in the art. Because of such surprising activity, such compound is also a particularly preferred compound of the present invention.

Finally, the present invention also provides pharmaceutical formulations comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

As used herein, the term "C_1-C_8 alkyl" represents a straight or branched alkyl chain having from one to eight carbon atoms. Typical C_1-C_8 alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, and the like. The term "C_1-C_8 alkyl" includes within its definition the terms "C_1-C_4

alkyl" and "C_1-C_8 alkyl".

"C_1-C_4 alkylphenyl" represents a straight or branched chain alkyl group having from one to four carbon atoms attached to a phenyl ring. Typical C_1-C_4 alkylphenyl groups include methylphenyl, ethylphenyl, n-propylphenyl, isopropylphenyl, n-butylphenyl, isobutylphenyl, and tert-butylphenyl.

The term "C_1-C_4 alkylthiophenyl" represents a straight or branched chain alkyl group having from one to four carbon atoms attached to a thiophenyl moiety. Typical C_1-C_4 alkylthiophenyl groups include methylthiophenyl, ethylthiophenyl, isobutylthiophenyl and the like.

In a similar fashion, the term "C_1-C_4 alkyloxyphenyl" represents a straight or branched chain alkyl group having from one to four carbon atoms attached to phenoxy moiety. Typical C_1-C_4 alkyloxyphenyl groups include methyloxyphenyl, ethyloxyphenyl, propyloxyphenyl and the like.

"C_1-C_8 alkoxy" represents a straight or branched alkyl chain having one to eight carbon atoms, which chain is attached to the remainder of the molecule by an oxygen atom. Typical C_1-C_8 alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, hexoxy, heptoxy, and the like. The term "C_1-C_8 alkoxy" includes within its definition the term "C_1-C_4 alkoxy".

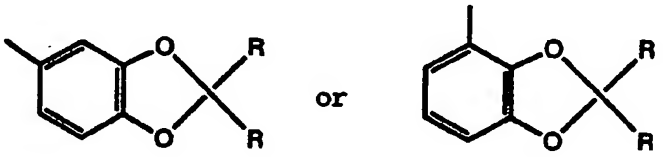
"C_1-C_8 alkylthio" represents a straight or branched alkyl chain having one to eight carbon atoms, which chain is attached to the remainder of the molecule by a sulfur atom. Typical C_1-C_8 alkylthio groups include methylthio, ethylthio, propylthio, butylthio, tert-butylthio, octylthio and the like. The term "C_1-C_8 alkylthio" includes within its definition the term "C_1-C_4 alkylthio".

The term "C_2-C_8 alkenyl" refers to straight and branched chain radicals of two to six carbon atoms, both inclusive, having a double bond. As such, the term includes ethylene, propylene, 1-butene, 2-butene, 2-methyl-1-propene, 1-pentene, 2-methyl-2-butene and the like.

The term "C_2-C_8 alkynyl" refers to straight and branched chain radicals of two to six carbon atoms, both inclusive, having a triple bond. As such, the term includes acetylene, propyne, 1-butyne, 2-hexyne, 1-pentyne, 3-ethyl-1-butyne and the like.

The term "C_3-C_8 cycloalkyl" refers to saturated alicyclic rings of three to eight carbon atoms, both inclusive, such as cyclopropyl, methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl and the like.

The terms "1,3-benzodioxanyl" and "substituted 1,3-benzodioxanyl" refer to structures of the formulae



where each R is independently hydrogen or C_1-C_4 alkyl.

"Quinolinyl" refers to a quinoline ring system which is attached to the rest of the molecule at the 4, 5, 6, 7 or 8 position of such ring system.

"N-substituted 2- or 3- indolyl" refers to a 2- or 3- indolyl ring system substituted on the nitrogen atom of that ring system with a C_1-C_8 alkyl, C_1-C_4 alkylphenyl, or C_3-C_8 cycloalkyl group.

The term "pharmaceutically acceptable salts" refers to salts of the compounds of the above formulae which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the above formulae with a pharmaceutically acceptable mineral or organic acid, or a pharmaceutically acceptable alkali metal or organic base, depending on the types of substituents present on the compounds of the formulae.

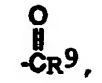
Examples of pharmaceutically acceptable mineral acids which may be used to prepare pharmaceutically acceptable salts include hydrochloric acid, phosphoric acid, sulfuric acid, hydrobromic acid, hydroiodic acid, phosphorous acid and the like. Examples of pharmaceutically acceptable organic acids which may be used to prepare pharmaceutically acceptable salts include aliphatic mono and dicarboxylic acids, oxalic acid, carbonic acid, citric acid, succinic acid, phenyl-substituted alkanoic acids, aliphatic and aromatic sulfonic acids and the like. Such pharmaceutically acceptable salts prepared from mineral or organic acids thus include hydrochloride, hydrobromide, nitrate, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, hydroiodide, hydrofluoride, acetate, propionate, formate, oxalate, citrate, lactate, p-toluenesulfonate, methanesulfonate, maleate, and the like.

Many compounds of formulae I, Ia or II which contain a carboxy, carbonyl, hydroxy or sulfoxide group may be converted to a pharmaceutically acceptable salt by reaction with a pharmaceutically acceptable alkali metal or organic base. Examples of pharmaceutically acceptable organic bases which may be used to prepare pharmaceutically acceptable salts include ammonia, amines such as triethanolamine, triethylamine, ethylamine,

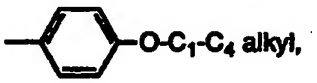
and the like. Examples of pharmaceutically acceptable alkali metal bases included compounds of the general formula MOR^{13}, where M represents an alkali metal atom, e.g. sodium, potassium, or lithium, and R^{13} represents hydrogen or C_1-C_4 alkyl.

It should be recognized that the particular anion or cation forming a part of any salt of this invention is not critical, so long as the salt, as a whole, is pharmacologically acceptable and as long as the anion or cationic moiety does not contribute undesired qualities.

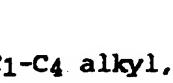
A preferred genus of compounds useful in the instantly claimed method of reducing blood glucose concentrations includes those compounds wherein Ar, R^1, R^2, R^3, m, R^4, and R^5 are as set forth for formula I, and R^6 is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, $-SO_2CH_3$ or $-(CH_2)_p$-Y where p is 0, 1, 2, or 3 and Y is cyano, $-OR^8$,



tetrazolyl, $NR^{10}R^{11}$, -SH, $-S(C_1$-C_4 alkyl), or



where R^8 is hydrogen, C_1-C_4 alkyl, or



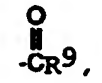
R^9 is hydrogen, C_1-C_4 alkyl, or NH_2; and R^{10} and R^{11} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, C_1-C_4 alkylphenyl, $-(CH_2)_qOH$, $-(CH_2)_qN(C_1$-C_4 alkyl$)_2$, or $-(CH_2)_qS(C_1$-C_4 alkyl) where q is 1 to 6, both inclusive, or R^{10} and R^{11}, taken together with the nitrogen atom to which they are attached, form a morpholinyl, piperidinyl, piperazinyl, or N-methylpiperazinyl ring .

Of this preferred genus, those compounds in which m is 0 are more preferred.

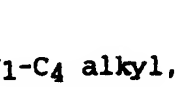
Of this more preferred genus, those compounds in which R^4 and R^5 taken together are =S are even more preferred.

Of this even more preferred genus, those compounds in which R^1 is hydrogen are especially preferred.

Of this especially preferred genus, those compounds in which R^6 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or $-(CH_2)_p$-Y where p is 0, 1, 2, or 3 and Y is $-OR^8$,



$-NR^{10}R^{11}$, or C_1-C_4 alkylthio, where R^8 is hydrogen, C_1-C_4 alkyl or



R^9 is hydrogen, C_1-C_4 alkyl or NH_2; and R^{10} and R^{11} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, or C_1-C_4 alkylphenyl are particularly preferred.

Of this particularly preferred genus, those compounds in which R^6 is hydrogen, C_1-C_6 alkyl, or C_2-C_6 alkenyl are more particularly preferred.

Of this more particularly preferred genus, those compounds in which Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, trifluoromethyl, C_1-C_4 alkylphenyl, phenyl, NO_2, F, Cl, hydroxy, phenoxy, C_1-C_4 alkyloxyphenyl, thiophenyl, C_1-C_4 alkylthiophenyl, $-COOR^7$, $-N(R^7)SO_2R^7$ or $-N(R^7)_2$, where each R^7 is independently hydrogen or C_1-C_6 alkyl, (iii) 2-, 3- or 4-pyridyl, or (iv) 2- or 3- furanyl are substantially preferred.

Of this substantially preferred genus, those compounds wherein Ar is phenyl substituted with from one to

three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_4 alkylphenyl, phenyl, NO_2, F, Cl, hydroxy, phenoxy, C_1-C_4 alkylthiophenyl, -$COOR^7$ or -$N(R^7)SO_2R^7$, where each R^7 is independently hydrogen or C_1-C_6 alkyl, are more substantially preferred.

Of this more substantially preferred genus, those compounds wherein Ar is phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl (especially C_1-C_4 alkyl), C_1-C_8 alkoxy (especially C_1-C_6 alkoxy), or hydroxy are even more substantially preferred.

The most preferred compounds which may be employed in the method of reducing blood glucose concentrations of the present invention include 5-[(3,4-diethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-pentoxy-phenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, sodium salt; 5-[(3-methoxy-4-pentoxyphenyl)methyl]-2-thioxo-4-thiazolidinone; 5[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-thioxo-4-thiazolidinone; 5[(3,5-dimethyl-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone and 5-[(3,5-dimethoxy-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone.

A preferred genus of compounds useful in the instantly claimed method of treating Alzheimer's disease includes those compounds wherein Ar, R^1, R^2, R^3, m, R^4 and R^5 are as set forth for formula Ia, and R^6 is hydrogen, C_1-C_6 alkyl or -$(CH_2)_pY$ where p is O, 1, 2 or 3 and Y is -$NR^{10}R^{11}$ where R^{10} and R^{11} are each independently hydrogen, C_1-C_6 alkyl, phenyl or C_1-C_4 alkylphenyl.

Of this preferred genus, those compounds in which m is O are more preferred.

Of this more preferred genus, those compounds in which R^4 and R^5 taken together are =S are even more preferred.

Of this even more preferred genus, those compounds in which R^2 and R^3 taken together form a bond are especially preferred.

Of this expecially preferred genus, those compounds in which Ar is phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, trifluoromethyl, C_1-C_4 alkylphenyl, phenyl, NO_2, F, Cl, hydroxy, phenoxy, C_1-C_4 alkyloxyphenyl, thiophenyl, C_1-C_4 alkylthiophenyl, -$COOR^7$, -$N(R^7)SO_2R^7$ or -$N(R^7)_2$, where each R^7 is independently hydrogen or C_1-C_4 alkyl, are particularly preferred.

Of this particularly preferred genus, those compounds in which R^1 is hydrogen are more particularly preferred.

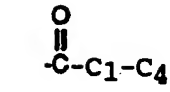
Of this more particularly preferred genus, those compounds in which Ar is phenyl substituted with from one to three substituents independently selected from phenoxy, phenyl, C_1-C_8 alkoxy, C_1-C_8 alkyl (especially C_1-C_4 alkyl), hydroxy, Cl, F, C_1-C_4 alkylthiophenyl, -$N(R^7)SO_2R^7$ and -$N(R^7)_2$, where each R^7 is independently hydrogen or C_1-C_6 alkyl, are substantially preferred.

The most preferred compounds which may be employed in the method of treating Alzheimer's disease of the present invention include 5-[(4-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[[(1,1'-biphenyl)-4-yl]methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-hexoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-heptoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-octoxyphenyl]methylene]-2-thioxo-4-thiazolidinone; 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-thioxo-4-thiazolidinone; 5-[(3,5-dichloro-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[[3-(1,1-dimethylethyl)-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone; and 5-[[4-(dimethylamino)phenyl]methylene]-2-thioxo-4-thiazolidinone.

A preferred genus of compounds of the present invention includes those compounds wherein Ar, R^1, R^2, R^3, R^4, R^5 and R^6 are as set forth for Formula II, and m is 0. Of this preferred genus, those compounds in which R^4 and R^5 taken together are =S are more preferred. Of this more preferred genus, those compounds in which R^2 and R^3 taken together form a bond are especially preferred.

Of this especially preferred genus, those compounds in which R^6 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or -$(CH_2)_p$-Y where p is 0, 1, 2, or 3 and Y is -OR^8,

-$NR^{10}R^{11}$, or C_1-C_4 alkylthio, where R^8 is hydrogen, C_1-C_4 alkyl or



R^9 is hydrogen, C_1-C_4 alkyl or NH_2; and R^{10} and R^{11} are each independently hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, phenyl, or C_1-C_4 alkylphenyl are particularly preferred.

Of this particularly preferred genus, those compounds in which R^6 is hydrogen, C_1-C_8 alkyl, or C_2-C_8 alkenyl are more particularly preferred. Of this more particularly preferred genus, those compounds in which R^1 is hydrogen or phenyl are even more particularly preferred.

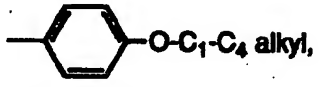
Of this even more particularly preferred genus, those compounds in which Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, trifluoromethyl, C_2-C_4 alkylphenyl, NO_2, F, Cl, phenoxy, C_1-C_4 alkoxyphenyl, thiophenyl, C_1-C_4 alkylthiophenyl, -$COOR^7$, -$N(R^7)SO_2R^7$ or -$N(R^7)_2$, where each R^7 is independently hydrogen or C_1-C_8 alkyl, (iii) 1,3-benzodioxanyl, (iv) substituted 1,3-benzodioxanyl or (v) quinolinyl are substantially preferred compounds.

Of this substantially preferred genus, those compounds wherein Ar is (i) phenyl substituted with from one to three of phenoxy or -$N(R^7)SO_2R^7$ where each R^7 is hydrogen or C_1-C_8 alkyl or (ii) 1,3-benzodioxanyl are more substantially preferred.

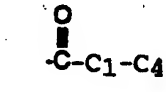
Certain preferred compounds of the present invention include 5-(diphenylmethylene)-2-thioxo-4-thiazolidinone; 5-[(1,3-benzodioxol-5-yl)methylene)-2-thioxo-4-thiazolidinone; 5-[(4-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-heptoxyphenyl)methylene]-3-amino-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-heptoxyphenyl)methylene]-3-dimethylamino-2-thioxo-4-thiazolidinone; and 5[(3-methanesulfonamidophenyl)methylene]-2-thioxo-4-thiazolidinone.

An alternative preferred genus of compounds of the present invention includes those compounds wherein Ar, R1, R^2, R^3, R^4, R^5, and m are as defined for formula II, and R^6 is C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, -SO_2CH_3 or -$(CH_2)_p$-Y where p is 0, 1, 2, or 3 and Y is cyano, -OR^8,

tetrazolyl, -$NR^{10}R^{11}$, -SH, C_1-C_4 alkylthio, or



where R^8 is hydrogen, C_1-C_4 alkyl, or



R^9 is hydrogen, C_1-C_4 alkyl, or NH_2; and R^{10} and R^{11} are each independently hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_6 alkynyl, phenyl, C_1-C_4 alkylphenyl, -$(CH_2)_qOH$, -$(CH_2)_qN(C_1$-C_4 alkyl$)_2$, or -$(CH_2)_qS(C_1$-C_4 alkyl) where q is 1 to 6, both inclusive, or R^{10} and R^{11}, taken together with the nitrogen atom to which they are attached, form a morpholinyl, piperidinyl, piperazinyl, or N-methylpiperazinyl ring.

Of this preferred genus, those compounds in which m is 0 are more preferred.

Of this more preferred genus, those compounds in which R^4 and R^5 taken together are =S are even more preferred.

Of this even more preferred genus, those compounds in which R^2 and R^3 taken together form a bond are especially preferred

Of this especially preferred genus, those compounds in which R^6 is C_2-C_8 alkenyl, or -$(CH_2)_p$-Y where p is 0, 1, 2, or 3 and Y is -OR^8,

$-NR^{10}R^{11}$, or C_1-C_4 alkylthio, where R^8 is hydrogen, C_1-C_4 alkyl or

C_1-C_4 alkyl, R^9 is hydrogen, C_1-C_4 alkyl or NH_2; and R^{10} and R^{11} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, or C_1-C_4 alkylphenyl are particularly preferred.

Of this particularly preferred genus, those compounds wherein R^1 is hydrogen or phenyl are more particularly preferred.

Of this more particularly preferred genus, those compounds in which Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, trifluoromethyl, C_2-C_4 alkylphenyl, NO_2, F, Cl, phenoxy, C_1-C_4 alkoxyphenyl, thiophenyl, C_1-C_4 alkylthiophenyl, $-COOR^7$, $-N(R^7)SO_2R^7$ or $-N(R^7)_2$, where each R^7 is independently hydrogen or C_1-C_6 alkyl (iii) 2-, 3- or 4-pyridyl, or (iv) 2- or 3- furanyl are even more particularly preferred.

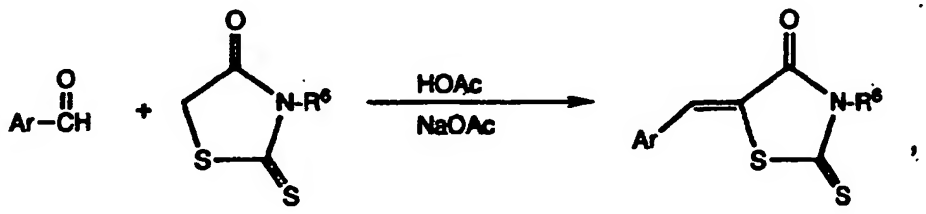
Of this even more particularly preferred genus, those compounds wherein Ar is phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, trifluoromethyl, C_2-C_4 alkylphenyl, NO_2, F, Cl, phenoxy, C_1-C_4 alkoxyphenyl, thiophenyl, C_1-C_4 alkylthiophenyl, $-COOR^7$, $-N(R^7)SO_2R^7$ or $-N(R^7)_2$, where each R^7 is independently hydrogen or C_1-C_6 alkyl, are substantially preferred.

Of this substantially preferred genus, those compounds wherein Ar is phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl or C_1-C_8 alkoxy are most preferred.

The present invention also encompasses formulations comprising a compound of the present invention in combination with a pharmaceutically acceptable carrier, diluent, or excipient therefor. Preferred formulations of the present invention are those formulations which contain a preferred compound or genus of compounds of the present invention, as described above.

The compounds of the present invention, as well as the compounds employed in the methods of the present invention, can, typically, be prepared by methods well known to one skilled in the art of organic chemistry. For example, such compounds may be prepared by condensation of rhodanine, or an appropriately substituted rhodanine derivative, with an appropriately substituted aromatic aldehyde or aldehyde derivative such as a mono or disubstituted imine of the formula

Such reaction is illustrated utilizing an appropriately substituted aromatic aldehyde as follows



where Ar and R^6 are as defined in formulae I, Ia and II.

Compounds of the present invention (as well as those compounds employed in the methods of the present invention) wherein R^2 and R^3 are hydrogen, or when taken together form a bond, and R^4 and R^5 are each hydrogen can be prepared by subjecting the compound wherein R^4 and R^5 taken together form =S to catalytic hydrogenation. The relative proportions of compound obtained (R^2, R^3, R^4 and R^5 all hydrogen vs. R^2 and R^3

taken together form a bond and R^4 and R^5 are hydrogen) depends upon the temperature, pressure, and duration of hydrogenation, the solvent employed and the particular catalyst used. Alternatively, the above transformations may be accomplished by heating the compounds wherein R^4 and R^5 taken together are =S and R^2 and R^3 taken together are a double bond in a mixture of hydrochloric acid and an alcohol, such as ethanol, in the presence of zinc. Reduction of the thione without affecting the benzylic double bond may be accomplished by heating the thione with a reducing agent such as tri-n-butyl tin hydride in a non-reactive solvent, such as toluene, and preferably in the presence of a free radical initiator, such as azobisisobutyronitrile. However, for such reduction to work, an N-substituted rhodanine substrate must be employed.

The transformation of compounds wherein R^2 and R^3 taken together form a bond and R^4 and R^5 taken together are =S to those compounds wherein R^2 and R^3 are both hydrogen while R^4 and R^5 remain unchanged may be accomplished by treating the unsaturated compound with a dihydropyridine, such as diethyl 2,6-dimethyl-1,4-dihydro-3,5-pyridine dicarboxylate in the presence of silica gel. The reaction is best carried out in the presence of a nonreactive solvent such as benzene or toluene, preferably under an inert atmosphere. The reaction may be accomplished at temperatures from about 25°C up to the reflux temperature of the mixture. At the preferred temperature of approximately 80°C, the reaction is essentially complete after about 12-18 hours.

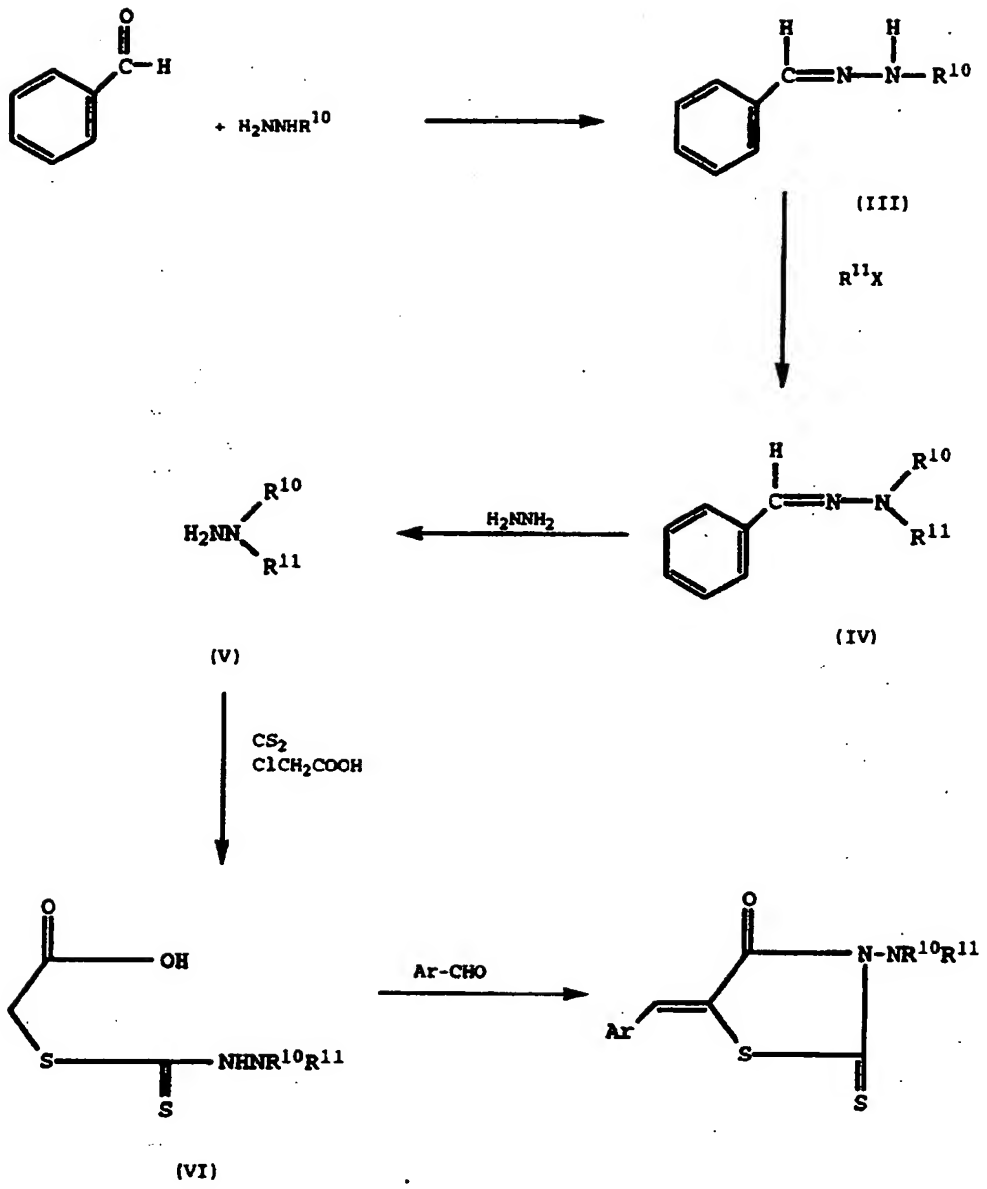
Compounds of formulae I, Ia or II wherein R^1 is C_1-C_6 alkyl, phenyl, a substituted phenyl of the type described above, or C_1-C_4 alkylphenyl may be prepared by conventional Friedel-Crafts acylation of an appropriately substituted aromatic compound with an acyl halide of the formula R^1-C(O)-X, wherein R^1 is as defined in formulae I or II and X is chloro, fluoro, bromo or iodo. The resulting aromatic ketone is then condensed with rhodanine, or an appropriately substituted rhodanine derivative.

The compounds of the present invention (as well as the compounds employed in the methods of the present invention) allow various R^6 substituents. These R^6 substituents can be prepared as follows.

Compounds of formulae I, Ia and II wherein R^6 is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl or -$(CH_2)_p$-Y where p is as defined for formulae I, Ia and II and Y is cyano, or $NR^{10}R^{11}$ where R^{10} and R^{11} are each independently hydrogen or C_1-C_6 alkyl may be prepared using the method set forth in the above reaction scheme. Alternatively, rhodanine may be used for condensation with an aldehyde or aldehyde derivative forming those species wherein R^6 is hydrogen, followed by alkylation or acylation with the appropriate R^6-containing halide. The alkylation or acylation is usually accomplished in an inert solvent such as tetrahydrofuran or dimethylformamide and in the presence of a strong base such as sodium hydride.

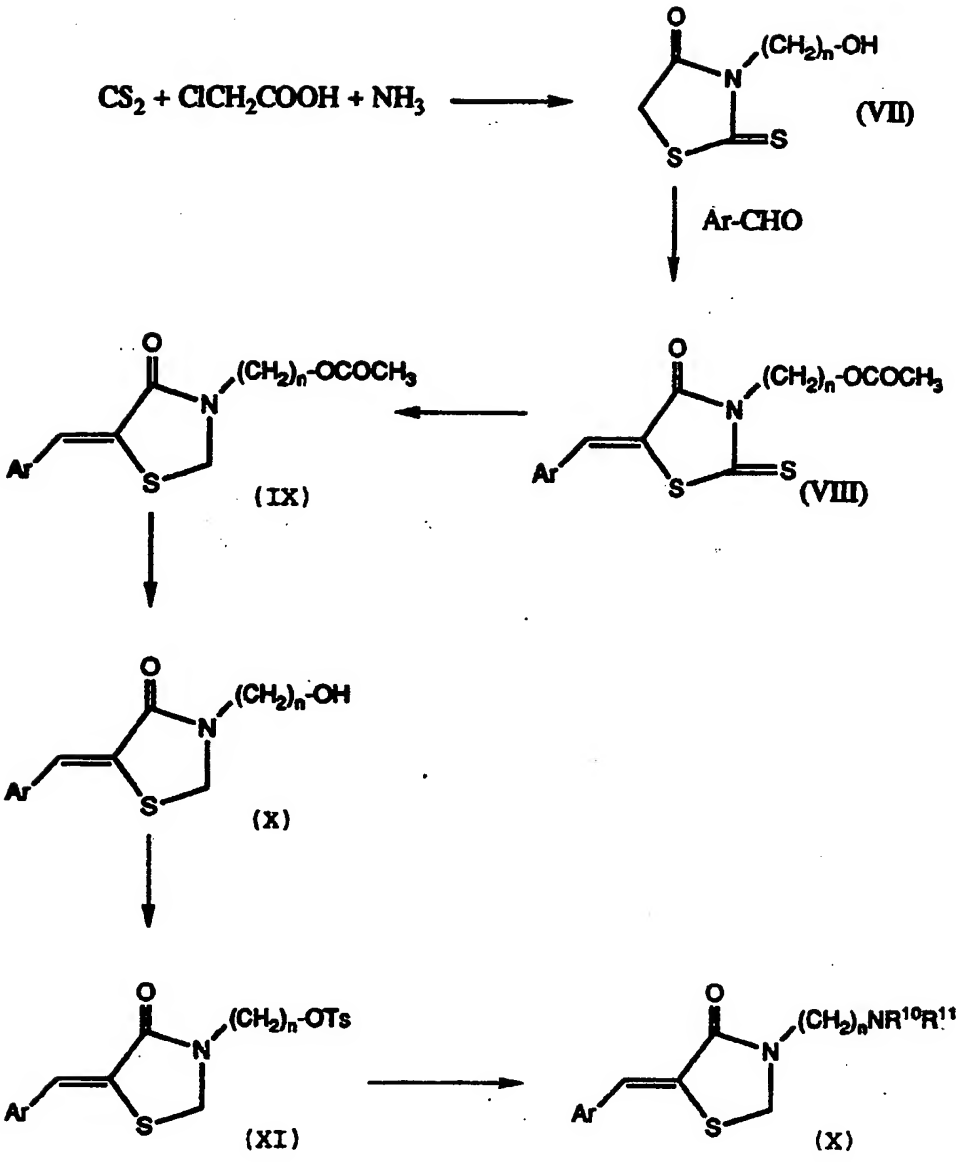
Alternatively, compounds of formulae I, Ia and II wherein R^6 is -$(CH_2)_p$-Y where Y is cyano may be prepared by treating the non-cyanated analog with a halo-substituted aliphatic nitrile. From this cyano derivative the tetrazolyl is prepared as by treatment with tri-N-butyl tin azide in, for example, ethylene glycol dimethyl ether.

Compounds of formulae I, Ia and II wherein R^6 is -$(CH_2)_p$-Y (p=0) and Y is $NR^{10}R^{11}$, where R^{10} and R^{11} are as defined in formulae I, Ia and II, may also be prepared by employing an appropriately substituted hydrazine. In this reaction sequence, benzaldehyde is reacted with an appropriately substitued hydrazine, in an alcoholic solvent, yielding III. An appropriately substituted alkyl halide is then reacted with III, in the presence of triethylamine and acetonitrile, to provide IV, which is then further reacted with hydrazine to yield the R^{10}, R^{11} hydrazine V. Compound V may alternatively be prepared by the reduction of a nitroso-$R^{10}R^{11}$ amine using zinc dust and acetic acid or aluminum and a strong base. The R^{10}, R^{11} hydrazine is then treated with carbon disulfide, chloroacetic acid and triethylamine to provide intermediate VI. Condensation of VI with an appropriately substituted aromatic aldehyde or aldehyde derivative yields the desired product, as represented by the following reaction scheme.



Furthermore, the thione portion of the compound produced above may be reduced by treatment with a reducing agent such as tri-n-butyltin hydride in an inert solvent such as toluene, preferably in the presence of a free radical initiator such as azobisisobutyronitrile. Preparation of compounds wherein one of R^{10} and R^{11} is hydrogen may be effected before or after reduction of the thione, as desired, by heating the disubstituted compound in a mixture of ethanol/water in the presence of a catalyst such as a rhodium catalyst.

Compounds of formulae I, Ia and II wherein R^6 is $-(CH_2)_p-Y$ and Y is OR^8 or $NR^{10}R^{11}$ (where R^8 is hydrogen, acetyl or tosyl and R^{10} and R^{11} are each independently hydrogen or C_1-C_6 alkyl) may also be prepared according to the following reaction scheme:



where Ts = Tosyl

A hydroxyalkyl rhodanine is prepared by condensing carbon disulfide, chloroacetic acid, and the appropriate hydroxyalkylamine by standard techniques. When condensed with the appropriately substituted aromatic aldehyde (or aldehyde derivative), as described above, the resulting product is the condensed 2-thioxo-4-thiazolidinone VIII which has been transformed into the acetyl derivative. The thioxo compound VIII may optionally be converted to the methylene compound of formulae I or II as described above. The acetyl group of intermediate IX may be removed upon treatment with aqueous ammonia in a solvent such as acetonitrile to provide compound X. The hydroxy compound X is then converted to the tosyl derivative upon treatment with p-toluenesulfonyl chloride in pyridine, preferably at temperatures of around 0°C. The versatile tosyl intermediate XI may then be transformed into the compounds of formulae I or II upon treatment with an appropriate $HNR^{10}R^{11}$ amine. This latter transformation is best accomplished by allowing XI to react in the presence of a molar excess of the amine. Once again, a solvent such as acetonitrile is useful for accomplishing this transformation.

Those compounds where m is 1 or 2 are readily prepared from the sulfide (m=0) by treatment with an oxidizing agent, such as m-chloroperbenzoic acid, in a suitable solvent for a time sufficient to generate the desired oxidative state.

Depending upon the definitions of R^1, R^2, and R^3, the compounds of formulae I, Ia and II may exist in va-

rious isomeric forms. The compounds, formulations and methods of the present invention are not related to any particular isomer but include all possible isomers and racemates.

It will be readily appreciated by one skilled in the art that the aromatic portion of the compounds of the invention (or the compounds employed in the methods of the present invention) can be provided by compounds which are either commercially available or may be readily prepared by known techniques from commercially available starting materials. Similarly, the rhodanine or N-substituted rhodanine starting material is either commercially available or may be prepared by well known methods from commercially available substrates.

The following Examples illustrate the preparation of the compounds of the present invention, as well as compounds which may be employed in the methods of the present invention. The Examples are illustrative only and are not intended to limit the scope of the instant invention in any way.

Example 1

5-[(3-methanesulfonamidophenyl)methylene]-2-thioxo-4-thiazolidinone

Thirty seven grams (185.9 mmol) of 3-methanesulfonamidbenzaldehyde, 25.0 g (187.9 mmol) of rhodanine, 48.0 g (585.3 mmol) of anhydrous sodium acetate and 950 ml of acetic acid were stirred while heating at reflux for 20 hours. The reaction was then stirred at room temperature for approximately another 60 hours. The resulting slurry was poured into 3000 ml of a 1:1 ethanol/water mixture. Solids precipitated and were recovered by filtration, washed with water and then vacuum dried to provide 54 g of title compound. m.p. 260-265°C.

Analysis for $C_{11}H_{10}N_2O_3S_3$			
Calculated:	C, 42.02;	H, 3.20;	N 8.91;
Found:	C, 42.15;	H, 3.57;	N 8.71.

Example 2

5-[(1,3-benzodioxol-5-yl)methylene]-2-thioxo-4-thiazolidinone

Twenty grams (133.2 mmol) of piperonal were reacted with 17.74 g (133.2 mmol)of rhodanine in 38.24 g (466.2 mmol) of glacial acetic acid at reflux for about 3 hours. The mixture was then poured into water and stirred overnight. A precipitate formed which was recovered by filtration and then air dried overnight to provide 27.8 g of title product. m.p. 194-195°C.

Analysis for $C_{11}H_7N_1O_3S_2$:				
Calculated:	C, 49.80;	H, 2.66;	N 5.28;	S, 24.17;
Found:	C, 50.04;	H, 2.38;	N 5.27;	S, 23.98.

Example 3

5-[(4-quinolinyl)methylene]-2-thioxo-4-thiazolidinone

Rhodanine (2.2 g; 16.5 mmol), 1.3 ml of concentrated ammonium hydroxide and 1 g of ammonium chloride in 20 ml of ethanol were heated on a steam bath for 15 minutes. 4-Quinoline carboxaldehyde (2.6 g; 16.5 mmol) was added and the resulting mixture was heated on the steam bath for another hour. Upon cooling to 5°C a precipitate formed. This precipitate was recovered by filtration and then washed with water to provide 4 g of title compound, m.p. 325-328°C.

Analysis for $C_{13}H_8N_2OS_2$:			
Calculated:	C, 57.33;	H, 2.96;	N 10.29;
Found:	C, 57.11;	H, 3.11;	N 10.21.

Example 4

5-(diphenylmethylene)-2-thioxo-4-thiazolidinone

One hundred and ninety grams (1.05 mol) of diphenyl ketimine, 140 grams (1.05 mol) of rhodanine, 5 ml of acetic acid and 1500 ml of toluene were heated at reflux for 3 hours. Crystals formed upon cooling. The solvent was decanted, fresh toluene was added to the residue and the resulting suspension was filtered. The recovered crystals were recrystallized from methanol to provide 172.0 g of title product, m.p. 192-194°C.

Analysis for $C_{16}H_{11}NOS_2$:				
Calculated:	C, 64.62; S, 21.56;	H, 3.73;	O, 5.38;	N 4.71;
Found:	C, 64.13; S, 22.38.	H, 3.84;	O, 5.57;	N 4.59;

Example 5

5-[(4-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

A mixture of 9.9 g (50.0 mmol) of 4-phenoxybenzaldehyde, 6.8 g (51.1 mmol) of rhodanine, 15.5 g of sodium acetate and 60 ml of acetic acid was heated on a steam bath for two hours. The reaction solution was then poured into water causing crude product to precipitate. The precipitate was filtered and then washed successively with water followed by diethyl ether to provide 8.6 g of title product, m.p. 195-200°C.

Analysis for $C_{16}H_{11}NO_2S_2$:			
Calculated:	C, 61.32;	H, 3.54;	N 4.47;
Found:	C, 61.07;	H, 3.63;	N 4.47.

The following compounds were synthesized using methods substantially equivalent to those described in Examples 1-5 above or as described elsewhere herein.

Example 6

5-(phenylmethylene)-2-thioxo-4-thiazolidinone, m.p. 202-203.5°C

Example 7

5-[(2-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 220-222°C

Example 8

5-[(4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 287-290°C

Example 9

5-[(2-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 197.5-199°C

Example 10

5-[(3-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 277-280°C

Example 11

5-[(3-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 242-244°C

Example 12

5-[(2,4-dimethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 253-255°C

Example 13

5-[(4-fluorophenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 225-227°C

Example 14

5-[(2-thienyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 231-233°C

Example 15

5-[(2-furanyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 217-219°C

Example 16

5-[(4-pyridyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 297-298°C

Example 17

5-[(3,4,5-trimethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 203-205°C

Example 18

5-[(4-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 252-254°C

Example 19

5-[(3,4,5-trimethoxyphenyl)methylmethylene]-2-thioxo-4-thiazolidinone, m.p. 210-213°C

Example 20

5-[(3-methoxy-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 229-231°C

Example 21

5-[(4-methoxyphenyl)phenylmethylene]-2-thioxo-4-thiazolidinone, m.p. 169-171°C

Example 22

5-[(3-pyridyl)methylene]-2-thioxo-4-thiazolidinone, m.p. ~286°C

Example 23

5-[(3-chlorophenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 233-235°C

Example 24

5-[(2,3-dimethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

Example 25

5-[(3-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

Example 26

5-[(2-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

Example 27

5-[(3-methyl-4-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

Example 28

5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-thioxo-4-thiazolidinone, m.p. ~260°C

Example 29

5-[(1,1'-biphenyl]-2-yl)methylene)-2-thioxo-4-thiazolidinone

Example 30

5-[(3-methoxy-4-hydroxyphenyl)methylene]-3-(2-propenyl)-2-thioxo-4-thiazolidinone, m.p. 146-148°C

Example 31

5-[(3-methoxy-4-heptoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 130-132°C

Example 32

5-[(3-ethoxy-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 217-217.5°C

Example 33

5-[(3-methylphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 197-202°C

Example 34

5-[(4-methylphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 229-234°C

Example 35

5-[(2-naphthalenyl)methylene)-2-thioxo-4-thiazolidinone, m.p. 224-225°C

Example 36

5-[(3,4-dichlorophenyl)methylene]-2-thioxo-4-thiazolidinone

Example 37

4-[(2-thioxo-4-thiazolidinone)methylene]benzoic acid, m.p. ~320°C

Example 38

5-[(3,4-diethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

Example 39

5-[(1H-indol-3-yl)methylene]-2-thioxo-4-thiazolidinone

Example 40

5-[(3-hydroxy-4-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 218-220°C

Example 41

5-[(3-methoxy-4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 175-176°C

Example 42

5-[[(1,1'-biphenyl)-4-yl]methylene]-2-thioxo-4-thiazolidinone, m.p. 245-250°C

Example 43

5-[(3-hydroxy-4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. ~224°C

Example 44

5-[(3-hydroxyphenyl)methylmethylene]-2-thioxo-4-thiazolidinone

Example 45

5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 170-171°C

Example 46

5-[(3-hydroxy-4-ethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. >225°C

Example 47

5-[(4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 158.5-160°C

Example 48

5-[(3-methoxy-4-ethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 207-207.5°C.

Example 49

5-[(3-ethoxy-4-propoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 156-157°C

Example 50

5-[(3-propoxy-4-ethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 186.5-188°C

Example 51

5-[(3,4-dipropoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 167.5-168.5°C

Example 52

5-[(3-methoxy-4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, sodium salt m.p. >225°C

Example 53

5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid, m.p. ~265°C

Example 54

5-[(3-methoxy-4-butoxyphenyl)methyl]-2-thioxo-4-thiazolidinone, m.p. 152-153.5°C

Example 55

5-[(3,5-dichloro-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. >260°C

Example 56

5-[(3-ethoxy-4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

Example 57

5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone sodium salt, m.p. ~254°C

Example 58

5-[(3-ethoxy-4-methoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. >225°C

Example 59

5-[[3,5-bis(1-methylpropyl)-4-hydroxyphenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid, m.p. 191-193°C

Example 60

5-[(3,4-dimethoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

Example 61

5-[(4-butoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 180°C

Example 62

5-[(3,5-dimethyl-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 260°C

Example 63

5-[(3,5-dimethoxy-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 230°C

Example 64

5-[(3-methoxy-4-pentoxyphenyl)methyl]-2-thioxo-4-thiazolidinone, m.p. 163-164°C

Example 65

5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-3-methyl-4-thiazolidinone, m.p. 117-118°C

Example 66

5-[(3-methoxy-4-pentoxyphenyl)methylene]-4-thiazolidinone, m.p. 174-175°C

Example 67

5-[(3-methoxy-4-pentoxyphenyl)methyl]-4-thiazolidinone, m.p. 108-109°C

Example 68

5-[(3-methoxy-4-hexoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

Example 69

5-[(3-methoxy-4-octoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 125-127°C

Example 70

5-[(3,5-dimethoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone, m.p. 166-167°C

Example 71

5-[[3-(1,1-dimethylethyl)-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone, m.p. 181-184°C

Example 72

5-[[3-ethoxy-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone, m.p. 190-192°C

Example 73

5-[[3-ethoxy-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-3-methyl-4-thiazolidinone, m.p. 137°C

Example 74

5-[[3-ethoxy-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-4-oxo-2-thioxo-3-thiazolidine acetic acid m.p. 202-206°C

Example 75

5-[(1-naphthyl)methylene]-2-thioxo-4-thiazolidinone, m.p.224-225°C

Example 76

5-[(2-naphthyl)methylmethylene]-2-thioxo-4-thiazolidinone

Example 77

5-[(3-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone

Example 78

5-[(3-phenoxyphenyl)methylmethylene]-2-thioxo-4-thiazolidinone

Example 79

5-[[3-(methyloxyphenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone, m.p. 177-180°C.

Example 80

5-[(3-methoxy-4-heptoxyphenyl)methylene]-2-thioxo-3-amino-4-thiazolidinone, m.p. 118-121°C (dec).

Example 81

5-[(3-methoxy-4-heptoxyphenyl)methylene]-2-thioxo-3-dimethylamino-4-thiazolidinone

Two hundred and fifty milligrams (1 mmol) of 3-methoxy-4-heptoxy benzaldehyde, 233 mg (1.2 mmol) of

2-(N-dimethylamino-dithiocarboxamido)acetic acid (a compound of formula VI, above), 330 mg (4 mmol) of anhydrous sodium acetate and 5 ml of acetic acid were stirred while heating at reflux for 15 hours. The reaction was then quenched by pouring the reaction solution into 10 ml of an ice/water mixture. The resulting solids were recovered by filtration, washed with ethyl acetate and then water to provide 450 mg of impure title compound. The impure compound was purified via recrystallization from hexane/methylene chloride to provide 180 mg of pure title compound. m.p. 105-108°C.

Example 82

5-[[4-(dimethylamino)phenyl]methylene]-2-thioxo-4-thiazolidinone

Example 83

5-[(4-heptoxyphenyl)methylene]-2-thioxo-3-dimethylamino-4-thiazolidinone, m.p. 80°C.

The present invention provides a method for lowering blood glucose levels in mammals comprising administering a therapeutically effective amount of a compound of formula I. The term "therapeutically effective amount", as defined herein, means the amount of compound necessary to provide a hypoglycemic effect following administration, preferably to a human susceptible to adult onset diabetes.

The hypoglycemic activity of the compounds of the present invention was determined by testing the efficacy of the compounds in vivo in male viable yellow obese-diabetic mice. The test procedure is described in detail below.

Test formulations were prepared by dissolving the test compound in a saline solution containing 2% Emulphor (a polyoxyethylated vegetable oil surfactant from GAF Corp.) to provide the dose level desired. Each test formulation was administered to six viable yellow obese-diabetic mice intraperitoneally at the beginning of the experiment. Blood glucose levels were determined immediately before the first dose and at 2 and 4 hours thereafter using glucose oxidase. A mean was taken of the 6 values obtained before the first dose and at the 2 and 4 hour intervals. The 2 and 4 hour mean values, calculated as a percentage of the first dose mean value, are reported in Table 1, below. In Table 1, Column 1 provides the example number of the test compound, Column 2 provides the dose level of compound tested, and Columns 3 and 4 provide a measurement of the test animal's blood glucose level 2 and 4 hours after test compound administration, respectively, as a percentage of the test animal's pre-administration blood glucose level.

TABLE 1

HYPOGLYCEMIC ACTIVITY OF TEST COMPOUNDS IN OBESE DIABETIC MICE

Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level	
		After 2 hrs.	After 4 hrs.
1	50	82 ± 5	75 ± 2
2	50	96 ± 1	82 ± 3
3	50	90 ± 10	73 ± 3
4	50	91 ± 4	72 ± 7
5	50	79 ± 4	71 ± 3
6	50	85 ± 6	72 ± 4
6	50	92 ± 4	79 ± 4
7	50	80 ± 4	91 ± 7
8	50	94 ± 4	84 ± 6
9	50	91 ± 8	83 ± 6
10	50	89 ± 4	80 ± 4
11	50	84 ± 3	85 ± 6
12	50	90 ± 7	69 ± 6
13	50	94 ± 4	88 ± 5
14	50	84 ± 7	71 ± 8
15	50	73 ± 5	62 ± 4
16	50	94 ± 8	96 ± 9
17	50	88 ± 8	89 ± 10
18	50	89 ± 4	88 ± 5
19	50	85 ± 14	75 ± 4
20	50	76 ± 3	70 ± 5
21	50	99 ± 4	81 ± 6
22	50	77 ± 5	67 ± 2

Table 1 (cont'd)

Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level	
		After 2 hrs.	After 4 hrs.
22	50	77 ± 6	69 ± 6
23	50	74 ± 6	90 ± 6
24	50	78 ± 4	80 ± 5
25	50	78 ± 4	74 ± 4
25	25	84 ± 5	87 ± 6
26	50	80 ± 4	75 ± 2
27	50	93 ± 3	84 ± 6
28	50	83 ± 9	79 ± 7
29	50	84 ± 5	77 ± 6
30	50	78 ± 7	81 ± 5
31	50	76 ± 7	76 ± 5
32	50	75 ± 4	80 ± 8
32	50	80 ± 18	66 ± 11
33	50	91 ± 6	86 ± 7
34	50	85 ± 8	79 ± 9
35	50	83 ± 5	85 ± 6
36	50	81 ± 7	90 ± 8
37	50	89 ± 4	80 ± 4
38	50	60 ± 5	59 ± 4
38	50	96 ± 6	80 ± 3
38	50	86 ± 4	81 ± 5
38	25	69 ± 9	65 ± 7
38	10	72 ± 4	71 ± 6
38	10	73 ± 8	59 ± 7
39	50	83 ± 4	76 ± 4
40	50	78 ± 5	72 ± 4

Table 1 (cont'd)

Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level	
		After 2 hrs.	After 4 hrs.
41	50	61 ± 3	51 ± 4
41	50	64 ± 6	54 ± 5
41	50	77 ± 5	62 ± 5
41	50	77 ± 5	72 ± 8
41	25	58 ± 6	45 ± 5
41	25	72 ± 7	64 ± 4
41	25	74 ± 7	70 ± 8
41	25	87 ± 5	85 ± 6
41	10	80 ± 7	59 ± 4
41	10	97 ± 7	75 ± 5
41	10	92 ± 7	92 ± 7
41	5	93 ± 10	71 ± 4
41	5	95 ± 4	97 ± 5
42	50	87 ± 8	70 ± 8
43	50	92 ± 7	88 ± 4
44	50	98 ± 4	88 ± 5
45	50	76 ± 7	57 ± 3
45	50	68 ± 2	66 ± 4
45	25	93 ± 4	87 ± 5
45	25	83 ± 10	78 ± 12
46	50	79 ± 4	77 ± 5
47	50	99 ± 14	76 ± 8
48	50	70 ± 3	65 ± 3
48	25	87 ± 4	81 ± 5
49	50	83 ± 5	77 ± 7
50	50	75 ± 5	69 ± 5
51	50	89 ± 7	85 ± 8

Table 1 (cont'd)

Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level After 2 hrs.	After 4 hrs.
52	50	73 ± 3	61 ± 4
53	100	83 ± 9	80 ± 14
53	50	73 ± 4	55 ± 5
54	50	76 ± 7	74 ± 6
55	50	81 ± 3	75 ± 3
56	50	78 ± 4	72 ± 3
56	25	81 ± 8	75 ± 3
56	10	94 ± 4	97 ± 4
57	50	63 ± 6	58 ± 7
57	50	69 ± 5	63 ± 7
57	25	67 ± 7	66 ± 7
57	25	79 ± 10	70 ± 4
57	10	95 ± 3	87 ± 6
57	5	82 ± 6	68 ± 5
58	50	67 ± 2	75 ± 5
59	50	62 ± 5	59 ± 9
60	50	85 ± 4	78 ± 3
60	50	102 ± 6	81 ± 5
60	25	87 ± 7	89 ± 6
61	50	76 ± 5	61 ± 5
61	50	98 ± 8	79 ± 4

The hypoglycemic activity of the compounds of the present invention was confirmed in a second in vivo test system; namely, the normal fed rat system. The procedure used in this test system is described below.

Male Sprague Dawley rats (Charles River Laboratories) weighing 175-200 g were used in this test system. Test formulations were prepared by suspending the test compound in 5% acacia (concentration of the drug was adjusted such that 0.25 ml/100 g body weight administered orally gave the desired dose on a body weight basis). The desired dose level of each test formulation was administered to four rats by oral gavage at the beginning of the experiment. Blood glucose levels were determined immediately before the first dose and at 3 and 5 hours thereafter by an enzymatic procedure employing glucose oxidase and peroxidase coupled with a chromogenic oxygen acceptor. A mean was taken of the 4 values obtained before the first dose and at the 3 and 5 hour intervals. The 3 and 5 hour mean values, calculated as a percentage of the first dose mean value, are reported in Table 2, below. In Table 2, Column 1 provides the example number of the test compound, Column 2 provides the dose level of compound tested, and Columns 3 and 4 provide a measurement of the test animal's blood glucose level 3 and 5 hours after test compound administration, respectively, as a percentage of the test animal's pre-administration blood glucose level.

TABLE 2

HYPOGLYCEMIC ACTIVITY OF TEST COMPOUNDS IN NORMAL FED RATS

Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level	
		After 3 hrs.	After 5 hrs.
15	167	84	87
16	200	92	79
17	200	78	68
22	200	84	68
24	200	100	100
25	200	100	100
26	200	100	100
31	200	95	92
32	200	100	96
38	200	90	74
41	160	76	67
45	167	61	63
47	200	82	73
48	167	87	81
49	200	100	98
56	150	79	65
57	200	84	73
58	200	100	100
61	200	89	82
62	200	78	53
63	200	69	52
64	200	91	89
65	200	100	91

Table 2 (cont'd)

Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level After 3 hrs.	After 5 hrs.
66	200	100	86
67	200	92	88
68	200	88	89
69	200	93	88

The hypoglycemic activity of the compounds of the present invention was confirmed in yet a third in vivo test system; namely, the obese diabetic Zucker rat (Zucker Diabetic Fatty Rat) test system. The rats used in this test system were 6 to 8 months old, weighed between 550 to 625 grams and had a pre-drug blood glucose level between 250 to 350 mg/dl. The procedure used in this test system is the same as that described for the normal fed rat test system, above. The results of such tests are set forth in Table 3, below. The format of Table 3 is the same as that used in Table 2.

TABLE 3

HYPOGLYCEMIC ACTIVITY OF TEST COMPOUNDS IN OBESE DIABETIC ZUCKER RATS			
Example # of Compound Tested	Dose (mg/kg)	Percent of Initial Blood Glucose Level	
		After 3 hrs.	After 5 hrs.
22	50	53	56
45	167	30	20
47	167	74	66
56	50	79	66

Finally, the long-term hypoglycemic activity of the compounds of the present invention was tested in yet another in vivo test system. This long-term test system entailed incorporating test compound into the test animal's diet at various concentrations (control animal's diet contained no test compound). Such diet was then fed to the test or control animals for either 14 or 21 days. Each test or control animal was then bled from the tail (200-400 µl sample of blood) at 0 (before diet started), 7, 14 and, if appropriate, 21 and 28 days after diet administration was started. Plasma samples were then obtained from each blood sample collected and the glucose concentration of such plasma samples was determined enzymatically.

The results of the long-term hypoglycemic test system described above are set forth in Table 4, below. In Table 4, Column 1 describes the type of rodent used in the test system, Column 2 provides the example number of the test compound or indicates that the numbers reported are for a control animal, Column 3 provides the concentration, in percent, of test compound in the test or control animal's diet. Columns 4-8 provide the plasma glucose concentration at days 0, 7, 14 and, if appropriate, 21 and 28, respectively, for the animals tested. Glucose lowering was not associated with depressed diet consumption.

TABLE 4

LONG-TERM HYPOGLYCEMIC ACTIVITY OF TEST COMPOUNDS

Type of Rodent*	Example No. of Cmpd. Tested	Concentration of Test Cmpd. in Diet (%)	Plasma Glucose Concentration (mg/dl) 0	7	14	21	28
ZDF	45	0.1	388	140	155	--	--
ZDF	control	--	416	364	445	--	--
ZDF	45	0.1	464	215	238	285	--
ZDF	45	0.025	467	451	452	517	--
ZDF	control	--	478	499	571	565	--
ZDF	45	0.1	357	171	166	--	--
ZDF	64	0.1	339	187	182	--	--
ZDF	control	--	343	423	454	--	--
ZDF	45	0.1	309	137	142	--	--
ZDF	71	0.1	311	237	232	--	--
ZDF	70	0.1	300	190	195	--	--
ZDF	control	--	317	286	255	--	--
Male A^{VY}/a (Harlan)	45	0.1	438	338	315	287	295
Male A^{VY}/a (Harlan)	38	0.1	340	351	328	303	331
Male A^{VY}/a (Harlan)	control	--	429	414	410	390	359

* ZDF = 8 week old male Zucker Diabetic Fatty rat; A^{VY}/a = viable yellow mouse

The present invention also provides a method for treating Alzheimer's disease in mammals comprising ad-

ministering a therapeutically effective amount of a compound of formula Ia. The term "therapeutically effective amount", as defined for this method, means the amount of compound necessary to reduce, eliminate or prevent the physiological effects or causes of Alzheimer's disease following administration, preferably to a human suffering from or susceptible to Alzheimer's disease.

Alzheimer's disease is a degenerative disorder of the human brain. Clinically, it appears as a progressive dementia. Its histopathology is characterized by degeneration of neurons, gliosis, and the abnormal deposition of proteins in the brain. Proteinaceous deposits (called "amyloid") appear as neurofibrillary tangles, amyloid plaque cores, and amyloid of the congophilic angiopathy. [For reviews, see, Alzheimer's Disease, (B. Reisberg, ed., The Free Press 1983).]

While there is no general agreement as to the chemical nature of neurofibrillary tangles, the major constituent of both the amyloid plaque cores and the amyloid of the congophilic angiopathy has been shown to be a 4500 Dalton protein originally termed β-protein or amyloid A4. Throughout this document this protein is referred to as β-amyloid peptide or protein.

β-amyloid peptide is proteolytically derived from a transmembrane protein, the amyloid precursor protein (APP). Different splice forms of the amyloid precursor protein are encoded by a widely expressed gene. see, *e.g.*, K. Beyreuther and B. Müller-Hill, Annual Reviews in Biochemistry, 58:287-307 (1989). β-amyloid peptide consists, in its longest forms, of 42 or 43 amino acid residues. J. Kang, et al., Nature (London), 325:733-736 (1987). These peptides, however, vary as to their amino-termini. C. Hilbich, et al., Journal of Molecular Biology, 218:149-163 (1991).

Because senile plaques are invariably surrounded by dystrophic neurites, it was proposed early that β-amyloid peptide is involved in the loss of neuronal cells that occurs in Alzheimer's disease. B. Yankner and co-workers were the first to demonstrate that synthetic β-amyloid peptide could be neurotoxic in vitro and in vivo. B. A. Yankner, et al., Science, 245:417 (1989); see also, N. W. Kowall, et al., Proceedings of the National Academy of Sciences. U.S.A., 88:7247 (1991). Other research groups, however, were unable to consistently demonstrate direct toxicity with β-amyloid peptide. see, *e.g.*, Neurobiology of Aging, 13:535 (K. Kosik and P. Coleman, eds. 1992). Even groups receiving β-amyloid peptide from a common source demonstrate conflicting results. D. Price, et al., Neurobiology of Aging, 13:623-625 (1991) (and the references cited therein).

As mentioned supra, cells have alternative mechanisms for processing APP which can result in the formation of the β-amyloid protein and subsequently, the senile plaques. It is likely that this alternative processing route occurs in the lysosomes. It has been found that compounds that inhibit lysosomal enzymes inhibit the fragment formation. see, *e.g.*, Science, 155:689 (1992).

A lysosome is a membranous reservoir of hydrolytic enzymes responsible for the intracellular digestion of macromolecules. Lysosomes are known to contain approximately forty hydrolytic enzymes, including proteases, nucleases, glycosidases, lipases, phospholipases, phosphatases and sulfatases. These enzymese are all acid hydrolases which are optimally active at about pH 5. Therefore, it is necessary to determine which enzyme or enzymes are responsible for this alternative processing of the APP and the consequent formation of the β-amyloid protein.

Abnormally high concentrations of the proteases cathepsins D and B have been observed in the brains of patients with early-onset Alzheimer's disease. Yu Nakamura, et al., Neuroscience Letters, 130, 195-198 (1991). Furthermore, elevated activity for cathepsin D has been observed in the brains of Alzheimer's patients. M. Takeda, et al., Neurochemistry Research, (abstract), 11:117 (1986). Cathepsin D is a lysosomal endoprotease that is present in all mammalian cells. see, *e.g.*, "Proteinases in Mammalian Cells and Tissues," ed. (A. J. Barret, ed. 1977) pp. 209-248. It is the only aspartyl protease that is known to be a lysosomal enzyme.

The cathepsins are a family of hydrolase enzymes that are usually located in the lysosomes. These enzymes are endopeptidases with an acidic optimum pH. Cathepsin A is a serine carboxypeptidase, cathepsin C [EC 3.4.14.1] is a dipeptidyl peptidase, cathepsin D [EC 3.4.23.5] is an aspartyl protease, and cathepsin B_2 [EC 3.4.16.1] is a serine carboxypeptidase. Cathepsin B [EC 3.4.22.1] (also known as cathepsin B_1) and cathepsin L [EC 3.4.22.15] are thiol proteases having activity within the lysosomes.

It has been found that inhibition of cathepsin D using an aspartyl protease inhibitor reduces the formation of β-amyloid protein and the resultant senile plaque. As such, compounds which inhibit cathepsins (and, in particular, cathepsin D) or reduce the formation of β-amyloid protein would be expected to be useful in treating Alzheimer's disease. Such activities were demonstrated in the following test systems.

CATHEPSIN D PERCENT INHIBITION ACTIVITY

A fluorometric assay was adapted from the method disclosed by Murakami et al., Anal. Biochem. 110:232-239 (1981) for measuring renin activity. Human liver cathepsin D (Athens Research and Technology, Athens, GA) was diluted in assay buffer, 200mM NaOAc, pH 4.5, 150mM NaCl to 500 ng/mL and then 100 µL of this

cathepsin D solution was added to each well of a 96 well plate with the exception of control wells which received just 100 µL of assay buffer. Compound stocks were prepared by dissolving a sufficient quantity of the particular compound to be tested in DMSO such that a 10 µg/ml concentration of test compound in DMSO was obtained and then 5 µL of the compound stock was added to each of the wells prepared above. Blank and enzyme control wells each received 5 µL of the DMSO vehicle.

Following a ten minute incubation at 25°C to allow enzyme/compound interaction, 5 µL of a 500µM solution of a derivative of a known porcine renin tetradecapeptide fluorometric substrate (Bachem Biosciences, Inc. 1993 Catalog ID No. I-1340; Bachem Biosciences, Philadelphia, PA) in DMSO was added per well to initiate the reaction. After incubation at 37°C for 30 minutes, cathepsin D activity was terminated by the addition of 100 µL per well of 400 mU/mL microsomal leucine aminopeptidase (EC 3.4.11.2, Sigma, St. Louis, MO) in 1M Tris-HCl, pH 8.0.

The plates were then analyzed in a fluorometer (CytoFluor 2350, Millipore, Bedford, MA) with an excitation wavelength of 360nm and an emission wavelength of 460nm, in order to check for background fluorescence due to test compounds. Following a two hour incubation at 37°C, to allow the aminopeptidase to release the fluorophore, 7-amido-4-methylcoumarin (AMC) from the products of cathepsin D cleavage, the plates were again analyzed in the fluorometer. In order to check for potential false positives, i.e., inhibitors of microsomal leucine aminopeptidase, residual aminopeptidase activity was monitored directly in each well by the addition of 20 µL/well of 2.5mM Leu-pNA (Bachem Biosciences, Philadelphia, PA) in 10% DMSO. Aminopeptidase activity was measured as an increase in the absorbance of 405nm in a UV_{max} microplate reader (Molecular Devices, Menlo Park, CA).

Cathepsin D activity was linear under these conditions and the results are expressed as a percentage of the controls in Table 5, below. All results presented are the mean and standard deviation of at least four replicate assays.

TABLE 5

CATHEPSIN D INHIBITION ACTIVITY	
Example No.	% Inhibition of Cathepsin D
1	36
4	50
5	74
6	29
8	64
18	38
42	88
45	62
50	40
55	90
75	43
76	32
77	87
81	21
82	79
82	68
83	47

CATHEPSIN D INHIBITION IC_{50} ACTIVITY

The above assay was repeated with the exception that the compound stocks were prepared in various concentrations other than 10 μg/ml so that IC_{50} values (concentration of test compound at which 50% inhibition of cathepsin D was obtained) for the test compounds could be determined. The results obtained from such assay system are set forth in Table 6 below.

TABLE 6

Example No.	IC_{50} (Mg/Ml
5	2.6
28	3.1
31	1.6
35	8.9
42	1.6
47	5.2
56	>4.15
68	3.4
68	1.4
69	2.4
71	1.2
71	4.8
77	4.5
78	25.0
79	3.7
80	47.0

β-AMYLOID PROTEIN PRODUCTION INHIBITION

Two cell lines (human kidney cell line 293 and Chinese hamster ovary cell line CHO) were stably transfected with the gene for APP751 containing the double mutation Lys-651-Met-652 to Asn-651-Leu-652 (APP-751 numbering) commonly called the Swedish mutation using the method described in Citron et al., Nature 360:672-674 (1992). The transfected cell lines were designated as 293 751 SWE and CHO 751 SWE, and were plated in Corning 96 well plates at $2.5x10^4$ or $1x10^4$ cells per well respectively in Dulbecco's minimal essential media (DMEM) plus 10% fetal bovine serum. Following overnight incubation at 37°C in an incubator equilibrated with 10% carbon dioxide (CO_2), the media were removed and replaced with 200 μL per well of conditioned media (media containing compound stocks; compound stocks diluted with media such that the concentration of DMSO in the media/compound stock solution did not exceed 0.5%) for a two hour pretreatment period during which the cells were incubated as described above. These compound stocks were prepared by dissolving a sufficient quantity of the particular compound to be tested in DMSO such that a 10 μg/ml concentration was obtained. After this pretreatment period, the conditioned media was removed and replaced with fresh conditioned media and the cells were incubated for an additional two hours.

After treatment, plates were centrifuged in a Beckman GPR at 1200 rpm for five minutes at room temperature to pellet cellular debris from the conditioned media. From each well, 100 μL of conditioned media were transferred into an ELISA plate precoated with antibody 266 [Seubert et al., Nature, 359:325-327 (1992)] and stored at 4°C overnight prior to the completion of the ELISA assay the next day.

Cytotoxic effects of the compounds were measured by a modification of the method of Hansen et al., J. Immun. Meth. 119:203-210 (1989). To the cells remaining in the tissue culture plate, was added 25 μL of a 3-

(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) stock solution (5 mg/mL) to a final concentration of 1 mg/mL. Cells were incubated at 37°C for one hour, and cellular activity was stopped by the addition of an equal volume of MTT lysis buffer (20% w/v sodium dodecylsulfate in 50% DMF, pH 4.7). Complete extraction was achieved by overnight shaking at room temperature. The difference in the OD_{562nm} and the OD_{650nm} was measured in a Molecular Devices UV_{max} microplate reader as an indicator of the cellular viability.

The results of the β-amyloid protein ELISA were fit to a standard curve and expressed as ng/mL β-amyloid protein peptide. In order to normalize for cytotoxicity, these β-amyloid protein results were divided by the cytotoxicity results and expressed as a percentage of the results from a drug-free control.

TABLE 7

β-AMYLOID PROTEIN INHIBITION	
Example No.	% Inhibition of β-Amyloid Protein
5	47
5	58
31	58
42	52
70	38
71	65
77	25
81	100

As can be seen from the data in Tables 5, 6 and 7, the compounds of formula Ia can be administered for prophylactic and/or therapeutic treatment of diseases related to the deposition of β-amyloid protein such as Alzheimer's disease, Down's syndrome, and advanced aging of the brain. In therapeutic applications, the compounds are administered to a host already suffering from the disease. The compounds will be administered in an amount sufficient to inhibit further deposition of β-amyloid protein plaque.

For prophylactic applications, the compounds of formula Ia are administered to a host susceptible to Alzheimer's disease or a β-amyloid protein related disease, but not already suffering from such disease. Such hosts may be identified by genetic screening and clinical analysis, as described in the medical literature. see e.g., Goate, Nature 349:704-706 (1991). The compounds will be able to inhibit or prevent the formation of the β-amyloid protein plaque at a symptomatically early stage, preferably preventing even the initial stages of the β-amyloid protein disease.

The compounds of the present invention and the compounds utilized in the methods of the present invention are effective over a wide dosage range. For example, dosages per day will normally fall within the range of about 0.5 to about 500 mg/kg of body weight. In the treatment of adult humans, the range of about 1.0 to about 100 mg/kg, in single or divided doses, is preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician in light of the relevant circumstances including the condition to be treated, the choice of compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms and the chosen route of administration. Therefore, the above dosage ranges are not intended to limit the scope of the invention in any way. While the present compounds are preferably administered orally, the compounds may also be administered by a variety of other routes such as the transdermal, subcutaneous, intranasal, intramuscular and intravenous routes.

While it is possible to administer a compound of the invention, or a compound used in the methods of this invention, directly, the compounds are preferably employed in the form of a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent or excipient and a compound of the invention. Such formulations will contain from about 0.01 percent to about 90 percent of a compound of the invention.

In making the formulations of the present invention, the active ingredient will usually be mixed with at least one carrier, or diluted by at least one carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the formulations can be in the form of tablets, granules, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium) and soft and hard gelatin capsules.

Examples of suitable carriers, diluents and excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, liquid paraffin, calcium silicate, microcrystalline cellulose, polyvinyl pyrrolidone, cellulose, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydroxybenzoates, vegetable oils, such as olive oil, injectable organic esters such as ethyl oleate, talc, magnesium stearate, water and mineral oil. The formulations may also include wetting agents, lubricating, emulsifying and suspending agents, preserving agents, sweetening agents, perfuming agents, stabilizing agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well-known in the art.

For oral administration, a compound of this invention, or a compound used in the methods of this invention, ideally can be admixed with carriers and diluents and molded into tablets or enclosed in gelatin capsules.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent or excipient therefor.

In order to more fully illustrate the operation of this invention, the following examples of formulations are provided. The examples are illustrative only and are not intended to limit the scope of the invention. The formulations may employ as active compounds any of the compounds of the present invention.

FORMULATION 1

Hard gelatin capsules suitable for use in treating Alzheimer's disease or reducing glucose concentration are prepared using the following ingredients:

	Amt. per Capsule	Concentration by Weight (percent)
Compound of Example No. 5	250 mg	55.0
Starch dried	220 mg	43.0
Magnesium stearate	10 mg	2.0
	460 mg	100.0

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

FORMULATION 2

Capsules each containing 20 mg of medicament are made as follows:

	Amt. per Capsule	Concentration by Weight (percent)
Compound of Example No. 1	20 mg	10.0
Starch	89 mg	44.5
Microcrystalline cellulose	89 mg	44.5
Magnesium stearate	2 mg	1.0
	200 mg	100.0

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve and filled into a hard gelatin capsule.

FORMULATION 3

Capsules each containing 100 mg of active ingredient are made as follows:

	Amt. per Capsule	Concentration by Weight (percent)
Compound of Example No. 45	100 mg	29.0
Polyoxyethylenesorbitan monooleate	50 mcg	0.02
Starch powder	250 mg	71.0
	250.05 mg	100.02

The above ingredients are thoroughly mixed and placed in an empty gelatin capsule.

FORMULATION 4

Tablets each containing 10 mg of active ingredient are made up as follows:

	Amt. per Capsule	Concentration by Weight (percent)
Compound of Example No. 71	10 mg	10.0
Starch	45 mg	45.0
Microcrystalline cellulose	35 mg	35.0
Polyvinyl pyrrolidone (as 10% solution in water)	4 mg	4.0
Sodium carboxyethyl starch	4.5 mg	4.5
Magnesium stearate	0.5 mg	0.5
Talc	1 mg	1.0
	100 mg	100.0

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granule so produced is dried at 50°-60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granule which, after mixing, is compressed on a tablet machine to yield a tablet weighing 100 mg.

FORMULATION 5

A tablet formula may be prepared using the ingredients below:

	Amt. per Capsule	Concentration by Weight (percent)
Compound of Example No. 2	250 mg	38.0
Cellulose microcrystalline	400 mg	60.0
Silicon dioxide fumed	10 mg	1.5
Stearic acid	5 mg	0.5
	665 mg	100.0

The components are blended and compressed to form tablets each weighing 665 mg.

FORMULATION 6

Suspensions each containing 5 mg of medicament per 40 ml dose are made as follows:

	Per 5 ml of suspension
Compound of Example No. 59	5 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Water	q.s. to 5 ml

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color is diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

FORMULATION 7

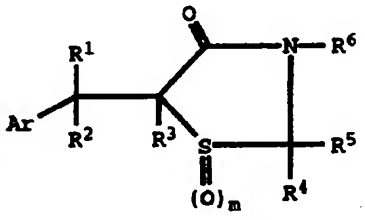
An aerosol solution is prepared containing the following components:

	Concentration by Weight (%)
Compound of Example No. 53	0.25
Ethanol	29.75
Propellant 22 (Chlorodifluoromethane)	70.00
	100.00

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted further with the remaining amount of propellant. The valve units are then fitted to the container.

Claims

1. The use of a compound of the formula



wherein:

Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, trifluoromethyl, C_1-C_4 alkylphenyl, phenyl, NO_2, F, Cl, hydroxy, phenoxy, C_1-C_4 alkyloxyphenyl, thiophenyl, C_1-C_4 alkylthiophenyl, -$COOR^7$, -$N(R^7)_2$ or -$N(R^7)SO_2R^7$, where each R^7 is independently hydrogen or C_1-C_6 alkyl, (iii) 1- or 2- naphthyl, (iv) 2- or 3-

benzofuranyl, (v) 2- or 3- benzothiophenyl, (vi) 2- or 3- thienyl, (vii) 2-, 3- or 4- pyridyl, (viii) 2- or 3- furanyl, (ix) 1,3-benzodioxanyl, (x) substituted 1,3-benzodioxanyl, (xi) quinolinyl, (xii) 2- or 3- indolyl or (xiii) N-substituted 2- or 3- indolyl;

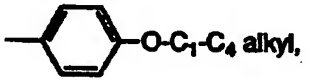
R^1 is C_1-C_6 alkyl, C_1-C_4 alkylphenyl, hydrogen, phenyl or phenyl substituted with one or two substituents independently selected from Cl, Br, F, I, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, trifluoromethyl, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$ or C_1-C_4 alkylthio;

R^2 and R^3 are each hydrogen or when taken together form a bond;

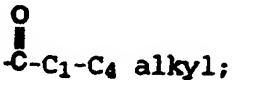
R^4 and R^5 are each hydrogen or when taken together are =S, or when one of R^4 and R^5 is hydrogen, the other is $-SCH_3$;

R^6 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, $-SO_2CH_3$, or $-(CH_2)_p$-Y where P is 0, 1, 2 or 3 and Y is cyano, $-OR^8$,

tetrazolyl, $-NR^{10}R^{11}$, -SH, C_1-C_4 alkylthio, or



where R^8 is hydrogen, C_1-C_4 alkyl, or



R^9 is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy or NH_2; and R^{10} and R^{11} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, C_1-C_4 alkylphenyl, $-(CH_2)_qOH$, $-(CH_2)_qN(C_1$-C_4 alkyl)$_2$, or $-(CH_2)_qS(C_1$-C_4 alkyl), where q is an integer from 1 to 6, both inclusive, or R^{10} and R^{11}, taken together with the nitrogen atom to which they are attached form a morpholinyl, piperidinyl, piperazinyl, or N-methylpiperazinyl ring;

m is 0, 1, or 2;

with the provisos that

Ar cannot be phenyl substituted solely with one chloro substituent at the 4-position of the phenyl ring;

Ar cannot be phenyl substituted with a COOH moiety at the 2-position of the phenyl ring;

when Ar is phenyl substituted with two ethoxy moieties at the 3- and 4-positions of the phenyl ring, R^1 must be hydrogen;

Ar cannot be phenyl substituted solely with two hydroxy substituents; and

when R^4 and R^5 are each hydrogen, R^6 cannot be C_1-C_6 alkyl,

or a pharmaceutically acceptable salt thereof, to prepare a medicament useful for reducing blood glucose concentrations in mammals.

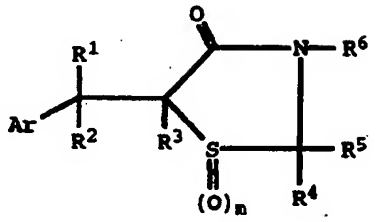
2. A use of Claim 1 which employs a compound wherein m is 0; R^4 and R^5 taken together are =S; R^1 is hydrogen; R^6 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl; and Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, trifluoromethyl, C_1-C_4 alkylphenyl, phenyl, NO_2, F, Cl, hydroxy, phenoxy, C_1-C_4 alkyloxyphenyl, thiophenyl, C_1-C_4 alkylthiophenyl, $-COOR^7$, $-N(R^7)SO_2R^7$ or $-N(R^7)_2$, where each R^7 is independently hydrogen or C_1-C_6 alkyl, (iii) 2-, 3- or 4- pyridyl, or (iv) 2- or 3- furanyl.

3. A use of Claim 2 wherein the compound employed is 5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical formulation adapted for reducing blood glucose concentrations comprising a compound as set forth in any one of Claims 1 through 3, admixed with one or more pharmaceutically acceptable

carriers, diluents or excipients therefor.

5. The use of a compound of the formula



wherein:

Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, trifluoromethyl, C_1-C_4 alkylphenyl, phenyl, NO_2, F, Cl, hydroxy, phenoxy, C_1-C_4 alkyloxyphenyl, thiophenyl, C_1-C_4 alkylthiophenyl, -$COOR^7$, -$N(R^7)_2$ or -$N(R^7)SO_2R^7$, where each R^7 is independently hydrogen or C_1-C_8 alkyl or (iii) 1- or 2- naphthyl;

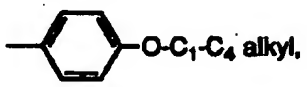
R^1 is C_1-C_6 alkyl, C_1-C_4 alkylphenyl, hydrogen, phenyl or phenyl substituted with one or two substituents independently selected from Cl, Br, F, I, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, trifluoromethyl, $-NH_2$, -$NH(C_1$-C_4 alkyl), -$N(C_1$-C_4 alkyl)$_2$ or C_1-C_4 alkylthio;

R^2 and R^3 are each hydrogen or when taken together form a bond;

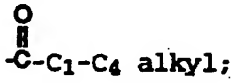
R^4 and R^5 are each hydrogen or when taken together are =S, or when one of R^4 and R^5 is hydrogen, the other is -SCH_3;

R^6 is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, -SO_2CH_3, or $(CH_2)_p$-Y where p is 0, 1, 2, or 3 and Y is cyano, -OR^8,

tetrazolyl, -$NR^{10}R^{11}$, -SH, C_1-C_4 alkylthio, or



where R^8 is hydrogen, C_1-C_4 alkyl, or



R^9 is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy or NH_2; and R^{10} and R^{11} are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, C_1-C_4 alkylphenyl, -$(CH_2)_q$OH, -$(CH_2)_q$N(C_1-C_4 alkyl)$_2$, or -$(CH_2)_q$S(C_1-C_4 alkyl), where q is an integer from 1 to 6, both inclusive, or R^{10} and R^{11}, taken together with the nitrogen atom to which they are attached form a morpholinyl, piperidinyl, piperazinyl, or N-methylpiperazinyl ring;

m is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof, to prepare a medicament useful in treating Alzheimer's disease.

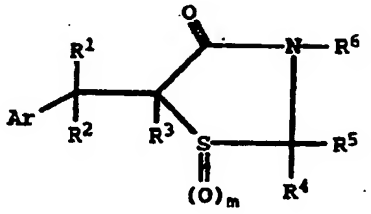
6. A use of Claim 5 which employs a compound wherein m is 0; R^4 and R^5 taken together are =S; R^1 is hydrogen; R^6 is hydrogen, C_1-C_6 alkyl, or -$(CH_2)_p$-Y where p is 0, 1, 2, or 3 and Y is -$NR^{10}R^{11}$ where R^{10} and R^{11} are each independently hydrogen, C_1-C_6 alkyl, phenyl or C_1-C_4 alkylphenyl; and Ar is phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, phenyl, F, Cl, hydroxy, phenoxy, C_1-C_4 alkylthiophenyl, -$N(R^7)SO_2R^7$ or -$N(R^7)_2$, where each R^7 is independently

hydrogen or C_1-C_6 alkyl.

7. A use of Claim 6 wherein the compound employed is selected from 5-[(4-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-phenoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[[(1,1'-biphenyl)-4-yl]methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-hexoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-heptoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[(3-methoxy-4-octoxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2-thioxo-4-thiazolidinone; 5-[(3,5-dichloro-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 5-[[3-(1,1-dimethylethyl)-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone; 5-[[4-(dimethylamino)phenyl]methylene]-2-thioxo-4-thiazolidinone or pharmaceutically acceptable salts thereof.

8. A pharmaceutical formulation adapted for treatment of Alzheimer's disease comprising a compound as set forth in any of Claims 5 through 7, admixed with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

9. A compound of the formula



wherein:

Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio, trifluoromethyl, C_2-C_4 alkylphenyl, NO_2, F, Cl, phenoxy, C_1-C_4 alkyloxyphenyl, thiophenyl, C_1-C_4 alkylthiophenyl, -$COOR^7$, -$N(R^7)_2$ or -$N(R^7)SO_2R^7$, where each R^7 is independently hydrogen or C_1-C_6 alkyl, (iii) 1- or 2- naphthyl, (iv) 2- or 3- benzofuranyl, (v) 2- or 3- benzothiophenyl, (vi) 2- or 3- thienyl, (vii) 2-, 3- or 4- pyridyl, (viii) 2- or 3- furanyl, (ix) 1,3-benzodioxanyl, (x) substituted 1,3-benzodioxanyl, (xi) quinolinyl, (xii) 2- or 3- indolyl or (xiii) N-substituted 2- or 3- indolyl;

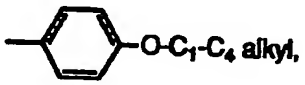
R^1 is C_1-C_6 alkyl, C_1-C_4 alkylphenyl, hydrogen, phenyl or phenyl substituted with one or two substituents independently selected from Cl, Br, F, I, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, trifluoromethyl, -NH_2, -$NH(C_1$-C_4 alkyl), -$N(C_1$-C_4 alkyl)$_2$ or C_1-C_4 alkylthio;

R^2 and R^3 are each hydrogen or when taken together form a bond;

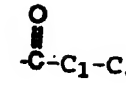
R^4 and R^5 are each hydrogen or when taken together are =S, or when one of R^4 and R^5 is hydrogen, the other is -SCH_3;

R^6 is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, -SO_2CH_3, or -$(CH_2)_p$-Y where p is 0, 1, 2, or 3 and Y is cyano, -OR^8,

tetrazolyl, -$NR^{10}R^{11}$, -SH, C_1-C_4 alkylthio, or



where R^8 is hydrogen, C_1-C_4 alkyl, or



R^9 is hydrogen, C_1-C_4 alkyl or NH_2; and R^{10} and R^{11} are each independently hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, phenyl, C_1-C_4 alkylphenyl, $-(CH_2)_qOH$, $-(CH_2)_qN(C_1$-C_4 alkyl$)_2$, or $-(CH_2)_qS(C_1$-C_4 alkyl), where q is an integer from 1 to 6, both inclusive, or R^{10} and R^{11}, taken together with the nitrogen atom to which they are attached form a morpholinyl, piperidinyl, piperazinyl, or N-methylpiperazinyl ring;

m is 0, 1, or 2;

with the provisos that

when Ar is (i) phenyl, (ii) phenyl substituted with from one to three substituents independently selected from C_1-C_8 alkyl, C_1-C_8 alkoxy, F, Cl, trifluoromethyl, phenoxy, C_1-C_4 alkyloxyphenyl, C_1-C_8 alkylthio, NO_2, $-N(R^7)_2$ or $-COOR^7$, where each R^7 is independently hydrogen or C_1-C_8 alkyl, (iii) 1- or 2-naphthyl, (iv) 2- or 3- benzofuranyl, (v) 2- or 3- benzothiophenyl, (vi) 2- or 3- thienyl, (vii) 2- or 3-indolyl, (viii) 2- or 3- furanyl, (ix) 2-, 3- or 4- pyridyl or (x) quinolinyl; R^1 is hydrogen or C_1-C_8 alkyl; R^2 and R^3 taken together form a bond; m is 0; and R^4 and R^5 taken together are =S, R^6 must be other than hydrogen or C_1-C_8 alkyl;

when Ar is phenyl; R^1 is hydrogen, methyl or ethyl; R^2 and R^3 taken together form a bond; m is 0; R^4 and R^5 taken together are =S; R^6 must be other than phenyl or C_1-C_4 alkylphenyl;

Ar cannot be phenyl substituted solely with one chloro substituent at the 4-position of the phenyl ring;

when Ar is phenyl substituted with two ethoxy moieties at the 3- and 4-positions of the phenyl ring, R^1 must be hydrogen;

Ar cannot be phenyl substituted with a COOH moiety at the 2-position of the phenyl ring; and

when R^4 and R^5 are each hydrogen, R^6 cannot be C_1-C_8 alkyl;

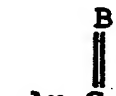
and the pharmaceutically acceptable salts thereof.

10. The compound 5-[(3-methoxy-4-pentoxyphenyl)methylene]-2-thioxo-4-thiazolidinone or a pharmaceutically acceptable salt thereof.

11. The compound 5-[[3-(1,1-dimethylethyl)-4-hydroxy-5-(methylthiophenyl)phenyl]methylene]-2-thioxo-4-thiazolidinone or a pharmaceutically acceptable salt thereof.

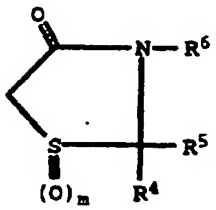
12. A pharmaceutical formulation comprising a compound of any one of Claims 9 through 11 associated with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

13. A process for preparing a compound as set forth in any of Claims 9-11 which comprises:
(A) reacting a compound of the formula



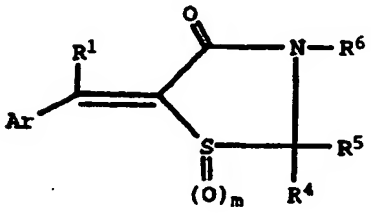
wherein:

B is O or NH and Ar and R^1 are as defined in any one of Claims 9, 10 or 11, with a compound of the formula



wherein:

R^4, R^5, m and R^6 are as defined in any one of Claims 9, 10 or 11, so as to provide a compound of the formula



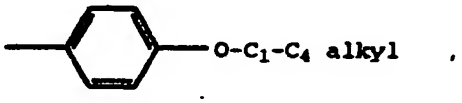
;

(B) reducing a compound of Claim 9 wherein R^4 and R^5 taken together are =S so as to prepare a compound of Claim 9 in which R^4 and R^5 are hydrogen;

(C) reducing a compound of Claim 9 in which R^2 and R^3 taken together form a bond so as to prepare a compound of Claim 9 in which R^2 and R^3 are hydrogen;

(D) reducing a compound of Claim 9 in which R^2 and R^3 taken together form a bond and R^4 and R^5 taken together are =S so as to prepare a compound of Claim 9 in which R^2, R^3, R^4 and R^5 are all hydrogen;

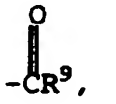
(E) alkylating a compound of Claim 9 in which R^6 is hydrogen so as to prepare a compound of Claim 9 in which R^6 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl or $-(CH_2)_p$-Y (where p is an integer from 0 to 3, both inclusive, and Y is cyano, OR^8, -SH, C_1-C_4 alkylthio, $-NR^{10}R^{11}$ or



,

where R^8 is as defined in Claim 9;

(F) acylating a compound of Claim 9 in which R^6 is hydrogen so as to prepare a compund of Claim 9 in which R^6 is $-(CH_2)_p$-Y, where p is an integer from 0 to 3, both inclusive, and Y is



,

where R^9 is as defined in Claim 9;

(G) oxidizing a compound of Claim 9 wherein m is 0, so as to prepare a compound of Claim 9 wherein m is 1;

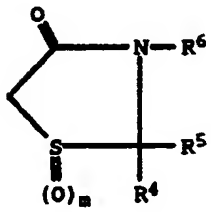
(H) oxidizing a compound of Claim 9 wherein m is 0, so as to prepare a compound of Claim 9 wherein m is 2;

(I) oxidizing a compound of Claim 9 wherein m is 1, so as to prepare a compound of Claim 9 wherein m is 2;

(J) reacting a compound of the formula

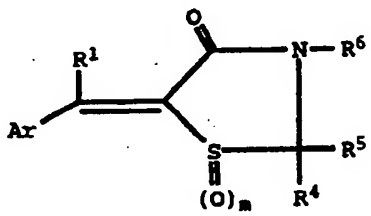
wherein:

B is O or NH and Ar and R^1 are as defined in Claim 9, with a compound of the formula



wherein

R^4, R^5 and m are as defined in Claim 9, and R^6 is $-(CH_2)_p-Y$ (where p is an integer from 0 to 3, both inclusive, and Y is OR^8, where R^8 is hydrogen) so as to provide a compound of the formula

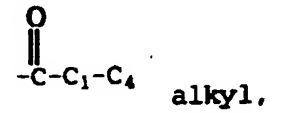


;

wherein:

Ar, R^1, R^4, R^5 and m are as set form in Claim 9 and R^6 is $-(CH_2)_p-Y$ (where p is an integer from 0 to 3, both inclusive, and Y is OR^8, where R^8 is

(K) reducing a compound of Claim 9 in which R^6 is $-(CH_2)_p-Y$, wherein p is 0 to 3, both inclusive, and Y is OR^8, where R^8 is



so as to prepare a compound of Claim 9 in which R^6 is $-(CH_2)_p-Y$, wherein p is 0 to 3, both inclusive, and Y is OR^8, where R^8 is hydrogen;

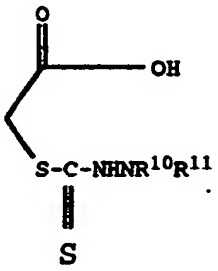
(L) reacting a compound of the formula set forth in Claim 9 in which R^6 is $-(CH_2)_p-Y$, wherein p is 0 to 3, both inclusive, and Y is OR^8, where R^8 is tosyl, with an amine of the formula $HNR^{10}R^{11}$ (where R^{10} and R^{11} are as defined in Claim 9) so as to prepare a compound of Claim 9 in which R^6 is $-(CH_2)_p-Y$, wherein p is 0 to 3, both inclusive, and Y is $-NR^{10}R^{11}$;

(M) treating a compound of Claim 9 in which R^6 is $-(CH_2)_p-Y$, wherein p is 0 to 3, both inclusive, and Y is cyano with tri-n-butyl tin azide so as to prepare a compound of Claim 9 in which R^6 is $-(CH_2)_p-Y$, wherein p is 0 to 3, both inclusive, and Y is tetrazolyl;

(N) reacting a compound of the formula

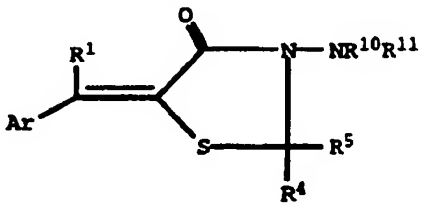
wherein:

B is O or NH and Ar and R^1 are as defined in Claim 9, with a compound of the formula



wherein:

R^{10} and R^{11} are as set forth in Claim 9, so as to provide a compound of the formula



wherein R^4 and R^5 taken together are =S and Ar, R^1, R^{10} and R^{11} are as defined in Claim 9;

(O) heating a compound of Claim 9 in which R^6 is $-(CH_2)_p-Y$ wherein p is 0 to 3, both inclusive, and Y is $-NR^{10}R^{11}$ (neither of R^{10} or R^{11} being hydrogen) in an ethanol/water mixture in the presence of a catalyst so as to prepare a compound of Claim 9 in which R^6 is $-(CH_2)_p-Y$ wherein p is 0 to 3, both inclusive, and Y is $-NR^{10}R^{11}$ (where one of R^{10} and R^{11} is hydrogen and the other is not hydrogen);

(P) salifying a compound of any one of Claims 9 through 11 by reacting the non-salt form of the compound with either a strong acid or a strong base.

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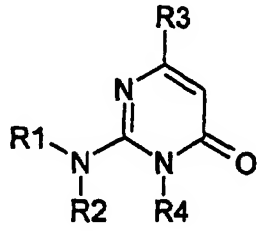
(54) 2-Amino-3-(alkyl)-pyrimidone derivatives as GSK3beta inhibitors

(57) A pyrimidone derivative represented by formula (I) or a salt thereof:



(I)

Wherein :

R1 represents a hydrogen atom or a C_{1-6} alkyl group;
R2 represents a C_{1-6} alkyl group which may be substituted, a C_{2-6} alkenyl group which may be substituted, a C_{3-6} alkynyl group which may be substituted, a C_{3-6} cycloalkyl group which may be substituted, or a C_{6-10} ARYL group which may be substituted;
or R1 and R2 form together a C_{2-6} alkylene group which may be substituted;
or R1 and R2 form together a chain of formula $-(CH_2)_2-X-(CH_2)_2-$ or $-(CH_2)_2-X-(CH_2)_3-$ where X represents a oxygen atom, a sulfur atom, or a nitrogen atom which may be substituted;
R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or a halogen atom; and
R4 represents a C_{1-6} alkyl group optionally substituted by a $C_{6,10}$ aryl group which may be substituted.

And a medicament comprising the said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a neurodegenerative disease caused by abnormal activity of GSK3β such as Alzheimer's disease, Parkinson's disease, frontoparietal dementia, corticobasal degeneration, Pick's disease, cerebrovascular accidents, brain and spinal trauma, and peripheral neuropathies.

EP 1 136 482 A1

Description

Technical Field

[0001] The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal activity of GSK3β.

Background Art

[0002] GSK3β (glycogen synthase kinase 3β) is a proline directed serine, threonine kinase that plays an important role in the control of metabolism, differentiation and survival. It was initially identified as an enzyme able to phosphorylate and hence inhibit glycogen synthase. It was later recognized that GSK3β was identical to tau protein kinase 1 (TPK1), an enzyme that phosphorylates tau protein in epitopes that are also found to be hyperphosphorylated in Alzheimer's disease and in several taupathies. Interestingly, protein kinase B (AKT) phosphorylation of GSK3β results in a loss of its kinase activity, and it has been hypothesized that this inhibition may mediate some of the effects of neurotrophic factors. Moreover, phosphorylation by GSK3β of β-catenin, a protein involved in cell survival, results in its degradation by an ubiquitinilation dependent proteasome pathway.

Thus, it appears that inhibition of GSK3β activity may result in neurotrophic activity. Indeed there is evidence that lithium, an uncompetitive inhibitor of GSK3β, enhances neuritogenesis in some models and also increases neuronal survival, through the induction of survival factors such as Bcl-2 and the inhibition of the expression of proapoptotic factors such as P53 and Bax.

Recent studies have demonstrated that β-amyloid increases the GSK3β activity and tau protein phosphorylation. Moreover, this hyperphosphorylation as well as the neurotoxic effects of β-amyloid are blocked by lithium chloride and by a GSK3β antisense mRNA. These observations strongly suggest that GSK3β may be the link between the two major pathological processes in Alzheimer's disease : abnormal APP (Amyloid Precursor Protein) processing and tau protein hyperphosphorylation.

Although tau hyperphosphorylation results in a destabilization of the neuronal cytoskeleton, the pathological consequences of abnormal GSK3β activity are, most likely, not only due to a pathological phosphorylation of tau protein because, as mentioned above, an excessive activity of this kinase may affect survival through the modulation of the expression of apoptotic and antiapoptotic factors. Moreover, it has been shown that β-amyloid-induced increase in GSK3β activity results in the phosphorylation and, hence the inhibition of pyruvate dehydrogenase, a pivotal enzyme in energy production and acetylcholine synthesis.

[0003] Altogether these experimental observations indicate that GSK3β may find application in the treatment of the neuropathological consequences and the cognitive and attention deficits associated with Alzheimer's disease, as well as other acute and chronic neurodegenerative diseases. These include, in a nonlimiting manner, Parkinson's disease, frontoparietal dementia, corticobasal degeneration, Pick's disease, cerebrovascular accidents, peripheral neuropathies, brain and spinal cord trauma.

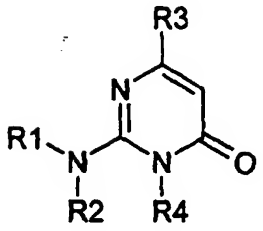
Disclosure of the Invention

[0004] An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables prevention and/or treatment of the diseases such as Alzheimer's.

Thus the inventors of the present invention have identified compounds possessing inhibitory activity against GSK3β.

As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases.

[0005] The present invention thus provides pyrimidone derivatives represented by formula (I) or salts thereof, solvates thereof or hydrates thereof:



(I)

Wherein :

R1 represents a hydrogen atom or a C_{1-6} alkyl group;
R2 represents a C_{1-6} alkyl group, which may be substituted, a C_{2-6} alkenyl group, which may be substituted, a C_{3-6} alkynyl group, which may be substituted, a C_{3-6} cycloalkyl group, which may be substituted, or a C_{6-10} ARYL group, which may be substituted;
or R1 and R2 form together a C_{2-6} alkylene group which may be substituted;
or R1 and R2 form together a chain of formula $-(CH_2)_2-X-(CH_2)_2-$ or $-(CH_2)_2-X-(CH_2)_3-$ where X represents a oxygen atom, a sulfur atom, or a nitrogen atom which may be substituted;
R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or a halogen atom; and
R4 represents a C_{1-6} alkyl group optionally substituted by a $C_{6,10}$ aryl group, which may be substituted.

[0006] According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives represented by formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by abnormal GSK3β activity, and the aforementioned medicament which is used for preventive and/or therapeutic treatment of neurodegenerative diseases. As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the diseases are selected from the group consisting of Alzheimer's disease, Parkinson's disease, frontoparietal dementia, corticobasal degeneration, Pick's disease, cerebrovascular accidents, brain and spinal cord trauma, and peripheral neuropathies and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives.

[0007] The present invention further provides an inhibitor of GSK3β activity comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

[0008] According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal GSK3β activity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

[0009] As used herein, the C_{1-6} alkyl group represents a straight or branched alkyl group having 1 to 6 carbon atoms, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, and the like;

[0010] The C_{2-6} alkylene group represents a divalent alkyl group;

[0011] The C_{2-6} alkenyl group represents an alkyl group having 2 to 6 carbon atoms and one or two double bond;

[0012] The C_{3-6} alkynyl group represents an alkyl group having 3 to 6 carbon atoms and one or two triple bond;

[0013] The C_{1-6} alkoxy group represents an alkyloxy group having 1 to 6 carbon atoms for example, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group, neopentyloxy group, 1,1-dimethylpropyloxy group and the like;

[0014] The halogen atom represents a fluorine, chlorine, bromine or iodine atom;

[0015] The C_{1-2} perhalogenated alkyl group represents an alkyl group wherein all the hydrogen have been substituted by a halogen atom, for example a CF_3 or C_2F_5;

[0016] The C_{1-3} halogenated alkyl group represents an alkyl group wherein at least one hydrogen has not been substituted by a halogen atom;

[0017] The $C_{6,10}$ aryl group represents a phenyl group, a naphth-1-yl group or a naphth-2-yl group;

[0018] The C_{6-10} ARYL group for R2 represents an indan-1-yl ring, an indan-2-yl ring tetrahydronaphthalen-1-yl ring, tetrahydronaphthalen-2-yl ring, a phenyl group, naphth-1-yl group or a naphth-2-yl group;

[0019] The $C_{6,10}$ aryloxy group represents a phenoxy group, a 1-naphthyloxy group or a 2-naphthyloxy group;

[0020] The C_{1-6} monoalkylamino group represents an amino group substituted by one C_{1-6} alky group, for example, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group and isopentylamino group;

[0021] The C_{2-12} dialkylamino group represents an amino group substituted by two C_{1-6} alkyl groups, for example, dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group and diisopropylamino group;

[0022] The heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10 represents, for example, a furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, furopyridine ring, isobenzofuran ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, thienopyridine ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, imidazopyridine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indolizine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, purine ring, quinolizine ring, quinoline ring, isoquinoline ring, phthalazine ring, naphtyridine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, dioxane ring, dithian ring, morpholine ring, thiomorpholine ring, phthalimide ring, tetrahydropyridoindole ring, tetrahydroisoquinoline ring, tetrahydrothienopyridine ring, tetrahydrobenzofuropyridine ring, and the like.

[0023] When R2 represents a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{3-6} alkynyl, a C_{3-6} cycloalkyl group which may be substituted, these groups may have 1 or 3 substituents selected form the group consisting of a C_{3-6} cycloalkyl, a C_{3-6} cycloalkyloxy group, a C_{1-6} alkoxy, a $C_{6,10}$ aryloxy group which may be substituted, hydroxyl group, a $C_{6,10}$ aryl group which may be substituted, a heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10 which may be substituted.

[0024] When a $C_{6,10}$ aryl group may be substituted, the $C_{6,10}$ aryl group may have 1 to 3 substituents selected from the group consisting of a C_{1-6} alkyl group, halogen atom, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a hydroxyl group, a C_{1-6} alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C_{1-6} monoalkylamino group, a C_{2-12} dialkylamino group, a (C_{1-6}-alkyl)carbonylamino group, a ($C_{6,10}$-aryl)carbonylamino group, a (C_{1-6}-alkoxy)carbonylamino group, aminocarbonyl group, a (C_{1-6}-monoalkylamino)carbonyl group, a (C_{2-12}-dialkylamino) carbonyl group, a formyl, a C_{1-6} alkylcarbonyl group, a ($C_{6,10}$-aryl)carbonyl group, a C_{1-6} alkylsulfonyl group, a $C_{6,10}$ arylsulfonyl group, aminosulfonyl group, a C_{1-6} monoalkylaminosulfonyl group, a C_{2-12} dialkylaminosulfonyl group, or a phenyl group;

[0025] Wherein the C_{1-6} alkyl groups and the C_{1-6} alkoxy groups are optionally substituted by a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group, an amino, a C_{1-6} monoalkylamino group, a C_{2-12} dialkylamino group, a (C_{1-6}-alkyl) carbonylamino group, a ($C_{6,10}$-aryl)carbonylamino group, a (C_{1-6}-alkoxy)carbonylamino group, a C_{1-6} alkylsulfonylamino group, a $C_{6,10}$ arylsulfonylamino group or a phenyl group.

[0026] When a C_{6-10} ARYL group may be substituted, the C_{6-10} ARYL group may have 1 to 3 substituents selected from the group consisting of a C_{1-6} alkyl group, halogen atom, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a hydroxyl group, a C_{1-6} alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C_{1-6} monoalkylamino group, a C_{2-12} dialkylamino group, a (C_{1-6} alkyl)carbonylamino group, a ($C_{6,10}$ aryl)carbonylamino group, a (C_{1-6} alkoxy)carbonylamino group.

[0027] When a $C_{6,10}$ aryloxy group may be substituted, the $C_{6,10}$ aryl group may have 1 to 3 substituents as defined above for the $C_{6,10}$ aryl group.

[0028] When the heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having a total ring-constituting atoms of 5-10, may be substituted, the heterocyclic ring may have 1 to 3 substituents selected from the group consisting of a C_{1-6} alkyl group, halogen atom, a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group, a hydroxyl group, a C_{1-6} alkoxy group, a nitro, a cyano, an amino, a C_{1-6} monoalkylamino group, a C_{2-12} dialkylamino group, a (C_{1-6}-alkyl)carbonylamino group, a ($C_{6,10}$ aryl)carbonylamino group, a (C_{1-6} alkoxy) carbonylamino group, aminocarbonyl group, a (C_{1-6} monoalkylamino)carbonyl group, a (C_{2-12} dialkylamino)carbonyl group, a formyl, a C_{1-6} alkylcarbonyl group, a ($C_{6,10}$ aryl)carbonyl group, a C_{1-6} alkylsulfonyl group, a $C_{6,10}$ arylsulfonyl group, aminosulfonyl group, a C_{1-6} monoalkylaminosulfonyl group, a C_{2-12} dialkylaminosulfonyl group, or a phenyl

group;

[0029] Wherein the C_{1-6} alkyl groups and the C_{1-6} alkoxy group being optionally substituted by a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group, an amino, a C_{1-6} monoalkylamino group, a C_{2-12} dialkylamino group, a (C_{1-6} alkyl) carbonylamino group, a ($C_{6,10}$ aryl)carbonylamino group, a (C_{1-6} alkoxy)carbonylamino group, a C_{1-6} alkylsulfonylamino group, a $C_{6,10}$ arylsulfonylamino group or a phenyl group.

[0030] When the C_{2-6} alkylene group may be substituted, the C_{2-6} alkylene group may have substituent 1 to 3 substituents selected from a group consisting of a C_{1-6} alkyl group which may be substituted by a $C_{6,10}$ aryl group which may be substituted, a C_{1-6} alkyl group which may be substituted by a heterocyclic ring which may be substituted, a $C_{6,10}$ aryl group which may be substituted, a heterocyclic ring which may be substituted; the substituents being as defined here above.

[0031] When R1 and R2 form together a chain of formula $-(CH_2)_2-X-(CH_2)_2-$ or $-(CH_2)_2-X-(CH_2)_3-$ wherein X represents a nitrogen atom which may be substituted, the group NR1R2 represents a piperazine ring or homopiperazine which may be substituted in position 4 by a substituent selected from the group consisting of a C_{1-6} alkyl group which may be substituted by a $C_{6,10}$ aryl group which may be substituted or by a heterocyclic ring which may be substituted; a $C_{6,10}$ aryl group which may be substituted or a heterocyclic ring which may be substituted, the substituents being as defined hereabove.

[0032] The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ-hydroxylysine, and arginine. The base-addition salts of acidic compounds are prepared by standard procedures well known in the art.

[0033] When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid.

[0034] The acid-addition salts of the basic compounds are prepared by standard procedures well know in the art which include, but are not limited thereto, dissolving the free base in an aqueous alcohol solution containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and an acid in an organic solvent, in which case the salt separates directly, or is precipitated with a second organic solvent, or can be obtained by concentration of the solution. The acids which can be used to prepare the acid-addition salts include preferably those which produce, when combined with the free base, pharmaceutically-acceptable salts, that is, salts whose anions are relatively innocuous to the animal organism in pharmaceutical doses of the salts, so that the beneficial properties inherent in the free base are not compromised by side effects ascribable to the anions. Although medicinally acceptable salts of the basic compounds are preferred, all acid-addition salts are within the scope of the present invention.

[0035] In addition to the pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The pyrimidone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S) configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers in pure form, any mixtures of stereoisomers, racemates and the like fall within the scope of the present invention.

[0036] Examples of preferred compounds of the present invention are shown in table 1 hereinafter. However, the scope of the present invention is not limited by these compounds.

[0037] Preferred compounds of the present invention represented by formula (I) include also:

(1) Compounds wherein R3 represents a 3- or 4-pyridyl group and more preferably 4-pyridyl group, which may be substituted by a C_{1-2} alkyl group, C_{1-2} alkoxy group or a halogen atom;
(2) R1 represents a hydrogen atom or a C_{1-6} alkyl group and R2 represents a C_{1-6} alkyl group which may be substituted, a C_{3-6} cycloalkyl group which may be subtituted, an indanyl group which may be subtituted;
(3) R1 and R2 form together a C_{2-6} alkylene group.

[0038] More preferred compounds of the present invention represented by formula (I) include also:

(1) Compounds wherein R3 represents an unsubstituted 4-pyridyl group; R1 represents a hydrogen atom or a
(2) R1 represents a hydrogen atom or a C_{1-6} alkyl group and R2 represents a C_{1-6} alkyl group substituted by a phenyl or substituted phenyl group, an indole ring or a substituted indole ring, a thiophene or substituted thiophene ring,

(3) R1 represents a hydrogen atom or a C_{1-6} alkyl group and R2 represents an indanyl group or an substituted indanyl group.

[0039] Particularly preferred compounds of the present invention represented by formula (I) include:

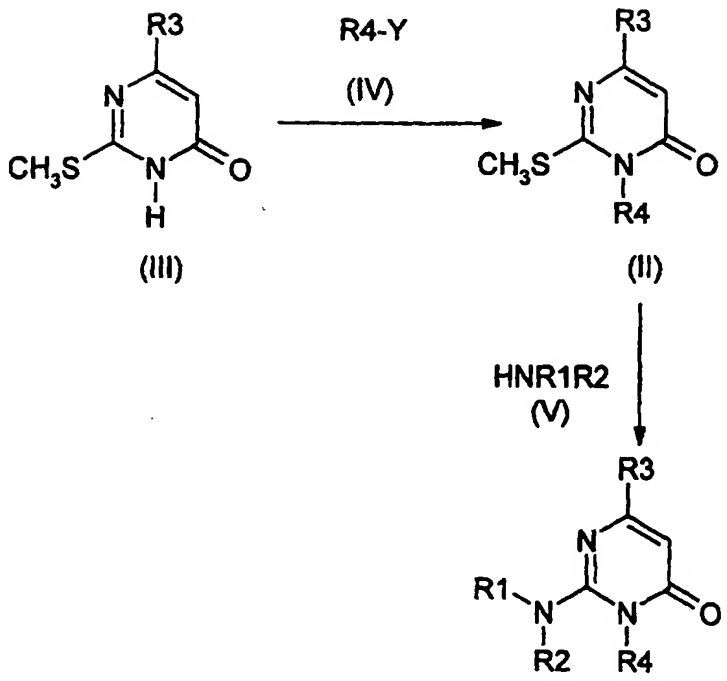
2-[[2-(phenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-methoxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(3-methoxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(2-methoxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(2-fluorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(3-fluorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-fluorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-bromophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(2-chlorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(2,4-dichlorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-aminophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(2,5-dimethoxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-chlorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-hydroxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-methylphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one
2-[[2-(4-aminosulfonylphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(3-chlorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(thiophen-2-yl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[4-(phenyl)butyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-phenylmethoxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-phenylphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[(phenylmethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[(2-methoxyphenyl)methyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(2,5-dimethoxyphenyl)ethyl]methylamino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[[3-(3-aminopropoxy)phenyl]methyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-4(3H)-one,
2-[[[3-(aminomethyl)phenyl]methyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[3-(phenyl)propyl]amino]-3-phenylmethyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(1H-indol-3-yl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(5-methoxy-1H-indol-3-yl)ethyl]amino]-3-methyl-6-pyndin-4-ylpyrimidin-4(3H)-one,
2-[[2-(5-phenylmethoxy-1H-indol-3-yl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(7-methyl-1H-indol-3-yl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(1-methyl-1H-indol-3-yl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(1-methyl-1H-indol-3-yl)ethyl]methylamino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-(cyclopentylamino)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-(ethylamino)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[(indan-2-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-(piperidin-1-yl)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-(pyrrolidin-1-yl)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one.

As a further object, the present invention concerns also methods for preparing the pyrimidone compounds represented by the aforementioned formula (I).
These compounds can be prepared, for example, according to the methods explained below.

1. Preparation Method 1

[0040] Pyrimidone compounds represented by the aforementioned formula (I) may be prepared according to scheme 1.

Scheme 1



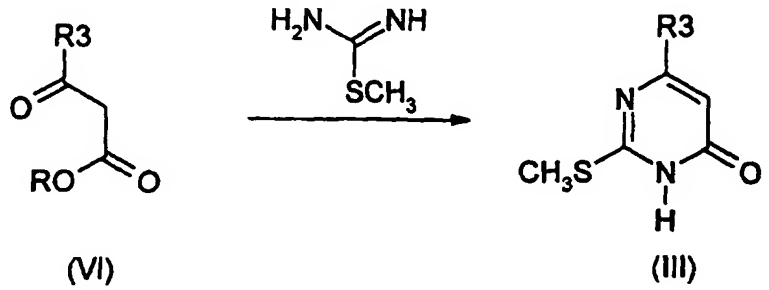
[0041] (In the above scheme the definition of R1, R2, R3 and R4 are the same as those already describe above for compounds of formula (I)).

[0042] The 2-methylthio derivative represented by the above formula (III), wherein R3 is as defined for compound of formula (I), is allowed to react with a compound of formula (IV), wherein Y represents a halogen atom such as for example a bromine or iodine in the presence of a base such as for example potassium carbonate, to obtain a compound of formula (II). The reaction may be carried out in aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like, at a suitable temperature ranging from -10 to + 20 °C under ordinary air.

[0043] Compound of formula (II) may then react with an amine of formula (V) to obtain the compound of the aforementioned formula (I). The reaction may be carried out in pyridine in presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), at a suitable temperature ranging from 25°C to reflux temperature.

[0044] Compound of formula (III) may be prepared according to the method defined in scheme 2.

Scheme 2



[0045] (In the above scheme R represents an alkyl group and the definition of R2 and R3 are the same as those already described for compound of formula (I).)

[0046] According to this method, the 3-ketoester of formula (VI) is allowed to react with a 2-methyl-2-thiopseudourea sulfate in the presence of a base such as potassium hydroxide. The reaction may be carried out in solvent such as water or an alcohol, such as ethanol, propanol and butanol, at a suitable temperature ranging from 25-100°C under ordinary air.

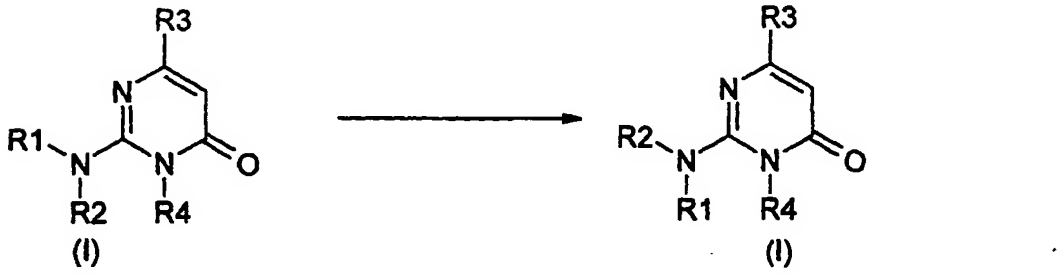
[0047] Compounds of formula (IV), (V) and formula (VI) are commercially available or may be synthesized according to known methods of one skilled in the art.

[0048] For example compounds of formula (VI), wherein R, R2 and R3 are as defined above, can be prepared by reacting a nicotinic acid optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or an halogen, with a malonic acid monoester. The reaction can be carried out using methods well known to one skilled in the art, such as for example in presence of a coupling agent such as 1,1'-carbonylbis-1H-imidazole in a solvent such as a tetrahydrofuran at a temperature ranging from 20 to 70°C.

2. Preparation method 2

[0049] Alternatively pyrimidone compounds represented by the aforementioned formula (I) may be prepared according to scheme 2.

Scheme 2



[0050] Compounds of formula (I) wherein R1 (and/or R2) represents a hydrogen atom, can be alkylated by methods well known to one skilled in the art such as, for example, by reacting (I), wherein R1 and/or R2 represents a hydrogen atom, with sodium hydride, in an aprotic polar such as dimethylacetamide or dimethylformamide at a temperature ranging from 0° to 10°. An alkylating agent such as an optionally substituted C_{1-6} alkyl halide is then added to obtain the compound of the above mentioned formula (I) wherein R1 and/or R2 represents an optionally substituted C_{1-6} alkyl alkyl group.

[0051] In addition when applicable, compound of formula (I) can be derivatised affording other compounds of formula (I), using well known methods in the art, for example when the $C_{6,10}$ aryl groups or the heterocyclic ring is substituted by a hydroxyl group, the hydroxyl group can be alkylated to give a C_{1-6} alkoxy group, or when the C_{6-10} ARYL group, the $C_{6,10}$ aryl group or the heterocyclic ring is substituted by an amino group or an aminoalkyl group, the amino function can be alkylated, acylated, etc... to give the corresponding derivatives.

[0052] In the above reactions, protection or deprotection of a functional group may sometimes be necessary. A suitable protecting group can be chosen depending on the type of a functional group, and a method described in the literature may be applied. Examples of protecting groups, of protection and deprotection methods are given for example in *Protective groups in Organic Synthesis* Greene et al., 2nd Ed. (John Wiley & Sons, Inc., New York).

[0053] The compounds of the present invention have inhibitory activity against GSK3β. Accordingly, the compounds of the present invention are useful as an active ingredient for the preparation of a medicament, which enables preventive and/or therapeutic treatment of neurodegenerative diseases such as Alzheimer's disease. In addition, the compounds

of the present invention are also useful as an active ingredient for the preparation of a medicament for preventive and/or therapeutic treatment of Parkinson's disease, frontoparietal dementia, corticobasal degeneration, Pick's disease, cerebrovascular accidents, brain and spinal cord trauma, and peripheral neuropathies.

[0054] The present invention further relates to a method for treating neurodegenerative diseases caused by abnormal activity of GSK3β and of the aforementioned diseases which comprises administering to a mammalian organism in need thereof an effective amount of a compound of the formula (I).

[0055] As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substances may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of another medicament for the treatment of the above mentioned diseases. A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

[0056] Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content ratios of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

[0057] Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

[0058] Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

Chemical Examples

[0059] The present invention will be explained more specifically with reference to the following general examples, however, the scope of the present invention is not limited to these examples.

Example 1 : Preparation of substituted 2-amino-3-methylpyrimidinones (method 1)

1.1. Preparation of Ethyl 3-(4-pyridyl)-3-oxopropionate

[0060] Isonicotinic acid (35.56 g, 289 mmol) was added to a solution of 1,1'-carbonylbis-1H-imidazole (46.98 g, 290 mmol) in tetrahydrofuran (700ml), and the resulting solution was stirred for 1.5 hr at 50°C. After cooling to room temperature, malonic acid monoester potassium salt (51.7 g, 304 mmol) and magnesium chloride (34.33 g, 361 mmol) were added, and the mixture was refluxed for 1 hr and then heated at 50°C for 6 hr. The solvent was removed under

reduced pressure and the residue was quenched by the addition of dilute acetic acid. The organic layer was extracted with ethyl acetate (3 times) and the combined extracts were washed with dilute aqueous sodium bicarbonate and brine, and were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; hexane/ethyl acetate = 2/1 to 1/1) and recrystallization from hexane - ethyl acetate gave 41.52 g (74%) of the title compound.

1.2. Preparation of 2-(Methylthio)-6-pyridinyl-4-ylpyrimidin-4(1H)-one

[0061] To a solution of 5.76 g (20.7 mmol) of 2-methyl-2-thiopseudolurea sulfate in 48 ml of water was added 4.85 g (86.52 mmol) of potassium hydroxide. The mixture was agitated and 8.0 g (41.4 mmol) of ethyl 3-(4-pyridyl)-3-oxo-propionate was added and stirring was maintained for 48 hours.
The precipitate was recovered by filtration and was washed with water and then ether. The product was dried at 90°C in vacuo to give 6.26 g, 69% of white solid.
Mp : 328-330°C.

1.3. Preparation of 3-methyl-2-(methylthio)-6-pyridin-4-yl-pyrimidin-4(3H)-one

[0062] To 3.0 g (13.7 mmol) of 2-methylthio-6-(4-pyridyl)pyrimidin-4-one in 50 ml of dimethylformamide was added 2.08 g (15.05 mmol) of potassium carbonate, followed by 0.85 ml (13.68 mmol) of methyl iodide at 0°C and stirring was maintained for 1.5 hours.
The reaction mixture was added to cold water and extracted with dichloromethane. The solvent was evaporated and the resulting solid was purified by chromatography on silica gel, eluting with a mixture of dichloromethane/methanol (99:1 to 90:10) to give 2.36 g, 78% of a white solid.
Mp. 176-178°C.

1.4. Preparation of substituted 2-amino-3-methylpyrimidinones

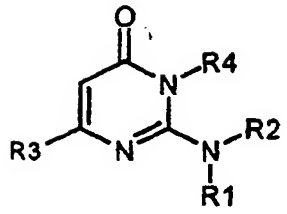
[0063] A solution of 1 equivalent of 3-methyl-2-(methylthio)-6-pyridin-4-yl-pyrimidin-(3H)-one and 1-5 equivalents of an amine of formula HNR4R5 were suspended in pyridine (0.1-1M) containing 3 equivalents of the DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and was refluxed 24 hours.
The cooled solution was treated with a saturated aqueous solution of ammonium chloride and extracted with dichloromethane. The organic layer was dried and evaporated to give crude product which was purified by chromatography on silica gel.

2. Preparation of substituted 2-alkylamino-3-alkylpyrimidinones (method 2)

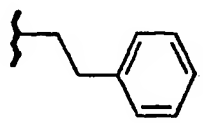
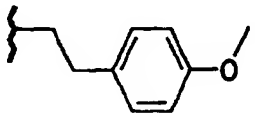
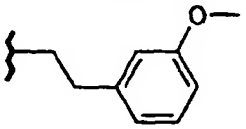
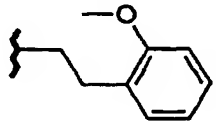
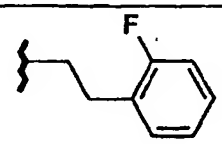
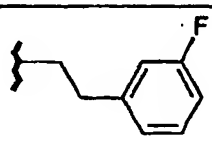
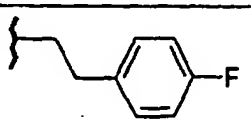
[0064] To a cooled (0°C) solution of substituted 2-amino-3-methylpyrimidinone (1 equivalent, 0.1 mole) in N,N-dimethylacetamide (0.35 ml) was added sodium hydride (0.11 mmole). The mixture was stirred for 5 min and alkyl iodide (0.1 mmole) was added, stirred for further 20 min at 0°C and the for 40 min at room temperature. Water (10 ml) was added, and the reaction mixture was extracted with ethyl acetate (3x 3 ml). The organic phases was separated, dried over sodium sulfate and evaporated to afford a residue which was purified by chromatograpy on silica gel.
[0065] A list of chemical structures and physical data for compounds of the aforementioned formula (I) illustrating the present invention is given in table 1. The compounds have been prepared according to the examples.

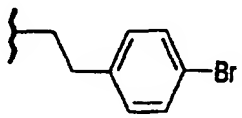
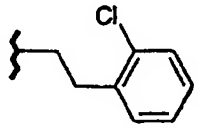
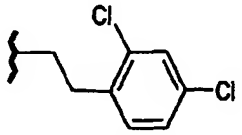
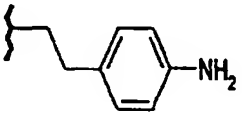
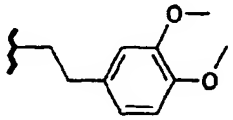
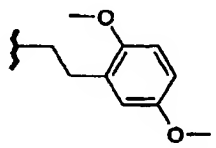
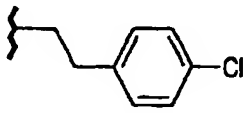
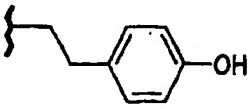
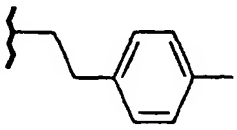
Table 1 : on following pages

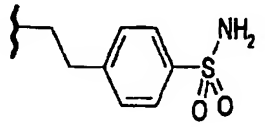
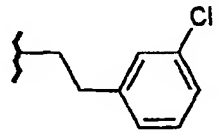
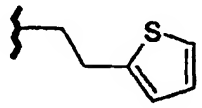
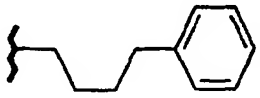
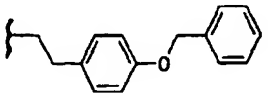
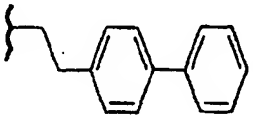
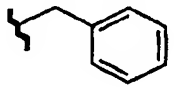
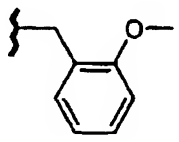
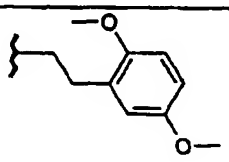
In the table : Me represents a methyl group
Ph represents an phenyl group

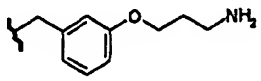
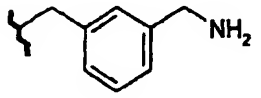
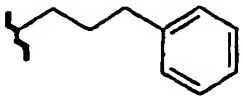
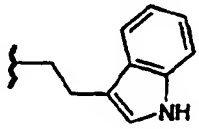
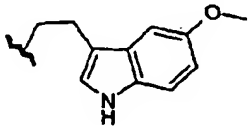
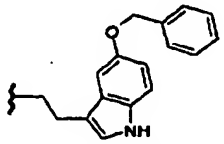
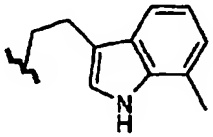
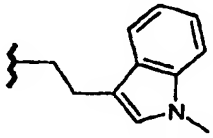
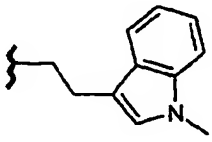


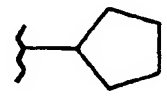
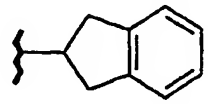
R3 = 4-pyridyl

No.	R1	R2	R4	m.p. (°C)	$[M+H]^+$
1	H		Me	186-187.5	307
2	H		Me	142.4-142.6	337
3	H		Me		337
4	H		Me	149.2-149.5	337
5	H		Me	184.0-187.2	325
6	H		Me	158.9-159.2	325
7	H		Me	178.8-178.9	325

8	H		Me	192.2-192.3	386
9	H		Me	175.2-175.4	341
10	H		Me	189.5-189.7	376
11	H		Me	197.3-197.5	322
12	H		Me	187.0-187.1	367
13	H		Me	180.9-181.3	367
14	H		Me	165.3-165.5	341
15	H		Me	257.4-257.9	323
16	H		Me	184.7-185	321

17	H		Me	-	386
18	H		Me	162.8-163	341
19	H		Me	171.7-171.9	313
20	H		Me	-	335
21	H		Me	169.7-169.8	413
22	H		Me	175.4-175.6	383
23	H		Me	-	293
24	H		Me	-	323
25	Me		Me	-	381

26	H		Me	193-196 (*)	-
27	H		Me	193-197 (*)	-
28			CH_2-Ph	218-221	-
29	H		Me	217-218 (**)	346
30	H		Me	242.7-243.0	376
31	H		Me	168.4-168.6	452
32	H		Me	217,2-217.3	360
33	H		Me	-	360
34	Me		Me	-	374

35	H		Me	-	271
36	H	Et	Me	239-241 (**)	231
37	H		Me	211.5-211.8	319
38	- (CH2)5 -		Me	228-230 (***)	271
39	- (CH2)4 -		Me	-	257

All compounds are bases, except (*) : dihydrochloride, (**) : oxalate and (***) : tartrate

Test Example: Inhibitory activity of the medicament of the present invention against GSK3β:

[0066] Two different protocols can be used.

[0067] In a first protocol : 7.5 µM of prephosphorylated GS1 peptide and 10 µM ATP (containing 300,000 cpm of 33P-ATP) were incubated in 25 mM Tris-HCl, pH 7.5, 0.6 mM DTT, 6 mM $MgCl_2$, 0.6 mM EGTA, 0.05 mg/ml BSA buffer for 1 hour at room temperature in the presence of GSK3beta (total reaction volume : 100 microliters).

[0068] In a second protocol : 4.1 µM of prephosphorylated GS1 peptide and 42 µM ATP (containing 260,000 cpm 33P-ATP) were incubated in 80 mM Mes-NaOH, pH 6.5, 1 mM Mg acetate, 0.5 mM EGTA, 5 mM 2-mercaptoethanol, 0.02% Tween 20, 10% glycerol buffer for 2 hours at room temperature in the presence of GSK3beta. Inhibitors were solubilised in DMSO (final solvent concentration in the reaction medium, 1%).

[0069] The reaction was stopped with 100 microliters of a solution made of 25 g polyphosphoric acid (85% P_2O_5), 126 ml 85% H_3PO_4, H_2O to 500 ml and then diluted to 1:100 before use. An aliquot of the reaction mixture was then transferred to Whatman P81 cation exchange filters and rinsed with the solution described above. Incorporated 33P radioactivity was determined by liquid scintillation spectrometry.

The phosphorylated GS-1 peptide had the following sequence :

NH2-YRRAAVPPSPSLSRHSSPHQS(P)EDEE-COOH.

[0070] The GSK3β inhibitory activity of the compounds of the present invention are expressed in IC_{50}, and as an illustration the range of IC_{50}'s of the compounds in table 1 is between 0.1 to 10 micromolar concentrations.

Formulation Example

(1) Tablets

[0071] The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

[0072] The ingredients below were mixed by an ordinary method and filled in soft capsules.

Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

(1) Parenteral preparations

[0073] The ingredients below were mixed by an ordinary method to prepare injections contained in a 1 ml ampoule.

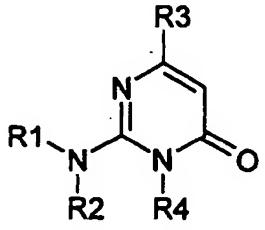
Compound of Example 1	3 mg
Sodium chloride	4 mg
Distilled water for injection	1 ml

Industrial Applicability

[0074] The compounds of the present invention have GSK3β inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal activity of GSK3β.

Claims

1. A pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



(I)

Wherein :

R1 represents a hydrogen atom or a C_{1-6} alkyl group;

R2 represents a C_{1-6} alkyl group which may be substituted, a C_{2-6} alkenyl group which may be substituted, a C_{3-6} alkynyl group which may be substituted, a C_{3-6} cycloalkyl group which may be substituted, or a C_{6-10} ARYL group which may be substituted;
or R1 and R2 form together a C_{2-6} alkylene group which may be substituted;
or R1 and R2 form together a chain of formula $-(CH_2)_2-X-(CH_2)_2-$ or $-(CH_2)_2-X-(CH_2)_3-$ where X represents a oxygen atom, a sulfur atom, or a nitrogen atom which may be substituted;
R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or a halogen atom; and
R4 represents a C_{1-6} alkyl group optionally substituted by a $C_{6,10}$ aryl group which may be substituted.

2. A pyrimidone derivative or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 1, wherein R3 represents an unsubstituted 4-pyridyl group.

3. A pyrimidone derivative or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 2, wherein R1 represents a hydrogen or a C_{1-6} alkyl group and R2 represents a C_{1-6} alkyl group which may be substituted, a C_{3-6} cycloalkyl group, an indanyl group which may be substituted;

4. A pyrimidone derivative or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 2, wherein R1 and R2 form together a C_{2-6} alkylene group.

5. A pyrimidone derivative or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 2, wherein R1 is an hydrogen or a C_{1-6} alkyl group and R2 represents a C_{1-6} alkyl group substituted by a phenyl or substituted phenyl ring, an indole ring or a substituted indole ring a thiophene or a substituted thiophene ring.

6. A pyrimidone derivative or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 3, wherein R1 is a hydrogen atom or a C_{1-6} alkyl group and R2 represents an indanyl group or an substituted indanyl group.

7. A pyrimidone derivative which is selected from the group consisting of:

2-[[2-(phenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-methoxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(3-methoxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(2-methoxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(2-fluorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(3-fluorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-fluorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-bromophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(2-chlorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(2,4-dichlorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-aminophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(2,5-dimethoxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-chlorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-hydroxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-methylphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one
2-[[2-(4-aminosulfonylphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(3-chlorophenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(thiophen-2-yl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[4-(phenyl)butyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-phenylmethoxyphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(4-phenylphenyl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[(phenylmethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[(2-methoxyphenyl)methyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(2,5-dimethoxyphenyl)ethyl]methylamino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[[3-(3-aminopropoxy)phenyl]methyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[[3-(aminomethyl)phenyl]methyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[3-(phenyl)propyl]amino]-3-phenylmethyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(1H-indol-3-yl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,

2-[[2-(5-methoxy-1 H-indol-3-yl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(5-phenylmethoxy-1H-indol-3-yl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(7-methyl-1H-indol-3-yl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(1-methyl-1H-indol-3-yl)ethyl]amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[[2-(1-methyl-1H-indol-3-yl)ethyl]methylamino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-(cyclopentylamino)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-(ethylamino)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-[(indan-2-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
2-(piperidin-1-yl)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one, and
2-(pyrrolidin-1-yl)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one,
or a salt thereof, or a solvate thereof or a hydrate thereof.

8. A medicament comprising as an active ingredient a substance selected from the group consisting of a pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 1.

9. A GSK3β inhibitor selected from the group of a pyrimidone derivative represented by formula (I) or salt thereof, or a solvate thereof or a hydrate thereof according to claim 1.

10. Use of a compound according to claim 1 to 7 for the preparation of a medicament for preventive and/or therapeutic treatment of a disease caused by abnormal GSK3β activity.

11. Use of a compound according to claim 1 to 7 for the preparation of a medicament for preventive and/or therapeutic treatment of a neurodegenerative disease.

12. Use of a compound according to claim 11, wherein the disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, frontoparietal dementia, corticobasal degeneration, Pick's disease, cerebrovascular accidents, brain and spinal cord trauma and peripheral neuropathies.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 40 0800

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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A	WO 98 24782 A (AMGEN INC.) 11 June 1998 (1998-06-11) * claims 1-31 *	1-12	
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	21 August 2000	Herz, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82